8540088

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

October 29, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: ***15/809,815***
FILING DATE: ***November 10, 2017***
PATENT NUMBER: ***11344552***
ISSUE DATE: ***May 31, 2022***

Certified by

Katherine Kelly Vidal

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

PTO/AIA/15 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	263266-421428
First Named Inventor	Eliel Bayever
Title	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

1. [✓] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✓] **Specification** [*Total Pages* 72] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✓] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 22]
6. **Inventor's Oath or Declaration** [*Total Pages* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✓] A copy from a prior application (37 CFR 1.63(d))
7. [✓] **Application Data Sheet** * *See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [ ] **37 CFR 3.73(c) Statement** *(when there is an assignee)* [✓] **Power of Attorney**
12. [ ] **English Translation Document** *(if applicable)*
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** *(MPEP § 503)* (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✓] **Other:** Certificate of Transmission

*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[ ] The address associated with Customer Number: _____ **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Cynthia M. Bott/	Date	November 10, 2017
Name (Print/Type)	Cynthia M. Bott, Ph.D.	Registration No. (Attorney/Agent)	46,568

Privacy Act Statement

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/241,106 filed on August 19, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Eliel Bayever Date (Optional): 11 Nov 2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ■ United States application or PCT international application number 15/241,106 filed on August 19, 2016.

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: Sarah F. Blanchette Date (Optional): 14 Nov 16

Signature: Sarah F. Blanchette

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Jonathan Basil Fitzgerald Date (Optional): 11/17/16

Signature: JBFitzgerald

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Daniel F. Gaddy Date (Optional): _____

Signature: _____

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/241,106 filed on August 19, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Bart S. Hendriks Date (Optional): 8-Nov-16

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/241,106

filed on August 19, 2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Ashish Kalra Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Privacy Act Statement

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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This declaration is directed to:

☐ The attached application, or

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filed on August 19, 2016.

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LEGAL NAME OF INVENTOR

Inventor: Helen Lee Date (Optional): Nov 23, 2016

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Docket No.: 263266-421428
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eliel BAYEVER et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: TBD

For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin | Examiner: TBD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(A)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on the 10th day of November 2017:

1. Utility Patent Application Transmittal Form (PTO/AIA/15);
2. Application Data Sheet (PTO/AIA/14);
3. Transmittal for Power of Attorney (PTO/AIA/82A) and Power of Attorney (PTO/AIA/80);
4. Application and Drawings;
5. Declarations for Utility Application Using an Application Data Sheet (PTO/AIA/01);
6. Fee Transmittal Form (PTO/SB/17); and
7. Certificate of Transmission under 37 C.F.R. § 1.8(a)

/Linda A. Zerby/
Linda A. Zerby (on behalf of Cynthia M. Bott, Reg. No. 46,568)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel BAYEVER
Filer:	Cynthia Marie Bott/Linda Zerby
Attorney Docket Number:	263266-421428

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1600**

Electronic Acknowledgement Receipt

EFS ID:	30921052
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel BAYEVER
Customer Number:	139696
Filer:	Cynthia Marie Bott/Linda Zerby
Filer Authorized By:	Cynthia Marie Bott
Attorney Docket Number:	263266-421428
Receipt Date:	10-NOV-2017
Filing Date:	
Time Stamp:	18:03:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1600
RAM confirmation Number	111317INTEFSW00015118503145
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	263266-421428_ADS.PDF	1846959 6c6257557ffd2632637a96e7e047b116fad8f408	no	11
Warnings:					
Information:					
2	Power of Attorney	263266-421428_POA.pdf	2097736 64045aacb7eb17e53a66b7114d0141aef52caf35	no	2
Warnings:					
Information:					
3		263266-421428_Application.pdf	1823398 677203ea2d302460e05e5ebc2fa9ca5b5cac81b4	yes	94

Multipart Description/PDF files in .zip description

Document Description	Start	End
Drawings-only black and white line drawings	73	94
Abstract	72	72
Claims	68	71
Specification	1	67

Warnings:					
Information:					
4	Fee Worksheet (SB06)	263266-421428_FeeTransmittal.pdf	2337837 10848daf6c72f7c8958e85a5326ceeb48e98c963	no	2
Warnings:					
Information:					

5	Transmittal of New Application	263266-421428_Transmittal.pdf	2303875 828c5c87f4561d55c3bb3de9eee9a7bec8bf2885	no	2
Warnings:					
Information:					
6	Oath or Declaration filed	263266-421428_Declarations.pdf	606774 1188dbbc598727474dda3280ba278963a5f5f8a6	no	14
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
7	Transmittal Letter	263266-421428_TransmissionCertificate.pdf	96272 bc993274f3296f917e92f2c2a9f19ab160d9c263	no	1
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	35259 69b93cb7319900017f96f947f1a06671c3e1fc36	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	11148110		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Eliel		Bayever	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
New York	NY	US

Mailing Address of Inventor:

Address 1	225 West 60th Street
Address 2	#PH1D

City	State/Province	Postal Code	Country
New York	NY	10023	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sarah	F.	Blanchette	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Lynnfield	MA	US

Mailing Address of Inventor:

Address 1	24 Edgemere Road
Address 2	

City	State/Province	Postal Code	Country
Lynnfield	MA	01940	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jonathan	Basil	Fitzgerald	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

City	Arlington	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	32 Magnolia Street
Address 2	

City	Arlington	State/Province	MA
Postal Code	02474	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniel	F.	Gaddy	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	250 Kendall Street, Apt. 707
Address 2	

City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bart	S.	Hendriks	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Belmont	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	225 Cross Street
Address 2	

City	Belmont	State/Province	MA
Postal Code	02478	Country	US

Inventor 6 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ashish		Kalra	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Belmont	State/Province	MA	Country of Residence	US

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Mailing Address of Inventor:

Address 1	19 Burnham Street, Apt. D2		
Address 2			
City	Belmont	**State/Province**	MA
Postal Code	02478	**Country**	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Helen		Lee	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Arlington	**State/Province**	MA	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	341 Park Avenue		
Address 2			
City	Arlington	**State/Province**	MA
Postal Code	02476	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	139696		
Email Address	patents@honigman.com	Add Email	Remove Email

Application Information:

Title of the Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin		
Attorney Docket Number	263266-421428	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	22	**Suggested Figure for Publication (if any)**	

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	139696		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15/241106	2016-08-19

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/343313	2016-05-31
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/323245	2016-04-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/302341	2016-03-02
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/281473	2016-01-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/273244	2015-12-30
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/216736	2015-09-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/241106	Claims benefit of provisional	62/208209	2015-08-21
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
● Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Ipsen Biopharm Ltd.		
Mailing Address Information For Applicant:			
Address 1	Ash Road, Wrexham Industrial Estate		
Address 2			
City	Wrexham	**State/Province**	
Country	GB	Postal Code	LL13 9UF
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Cynthia M. Bott/			Date (YYYY-MM-DD)	2017-11-10
First Name	Cynthia	Last Name	Bott	Registration Number	46,568

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	263266-421428
	Application Number	
Title of Invention	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: PA..
Document Description: Power of Attorney

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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	TBD
Filing Date	November 10, 2017
First Named Inventor	Eliel BAYEVER
Title	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	263266-421428

SIGNATURE of Applicant or Patent Practitioner

Signature	/Cynthia M. Bott/	Date (Optional)	November 10, 2017
Name	Cynthia M. Bott, Ph.d	Registration Number	46568
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 139696

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

IPSEN BIOPHARM LTD.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Janice M. Klunder	Date (Optional)	1-May-2014
Name	Janice M. Klunder, Ph.D., J.D.		
Title	Vice President, Intellectual Property, Endocrinology and R&D Peptides		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

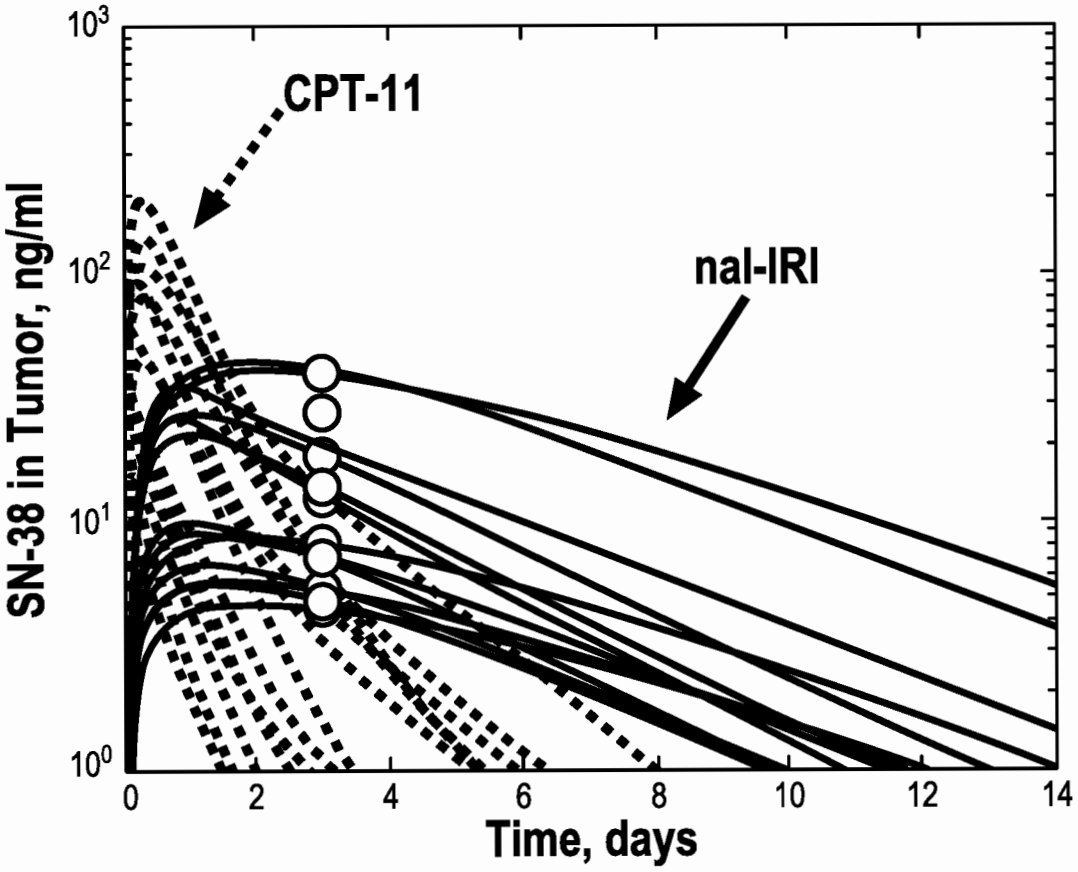


FIG. 1A

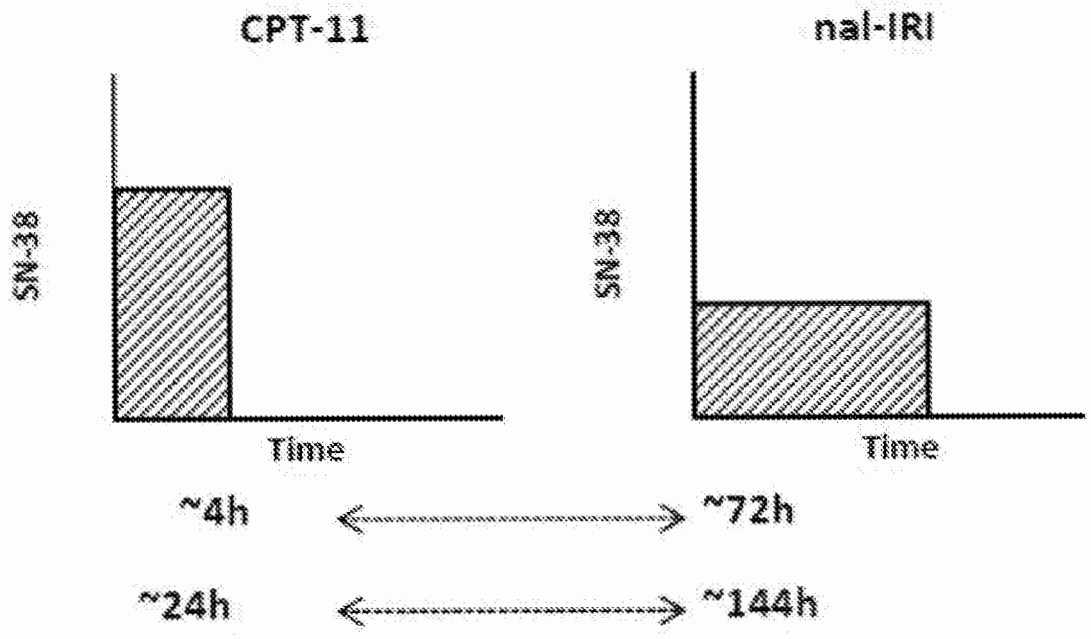


FIG. 1B

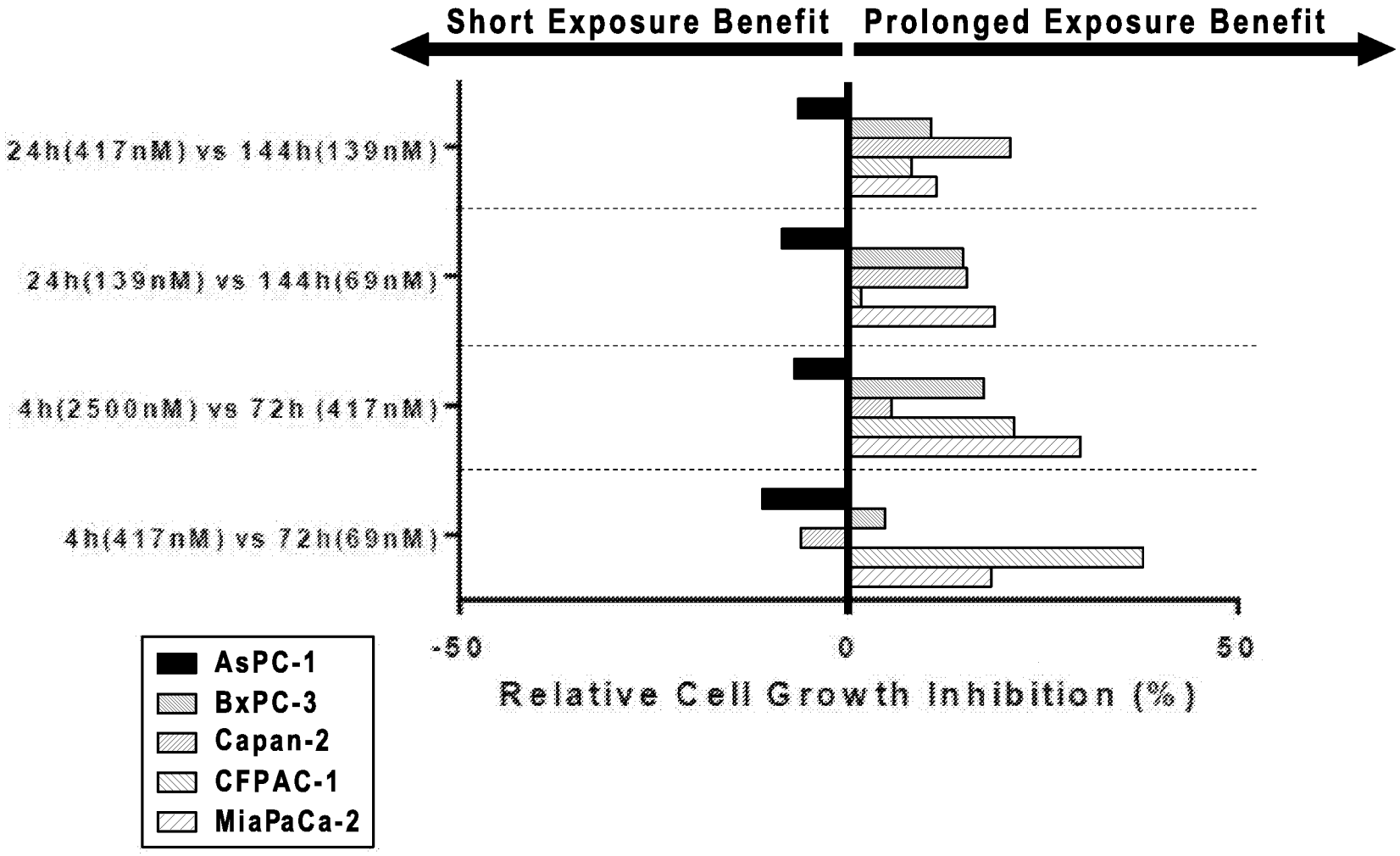


FIG. 1C

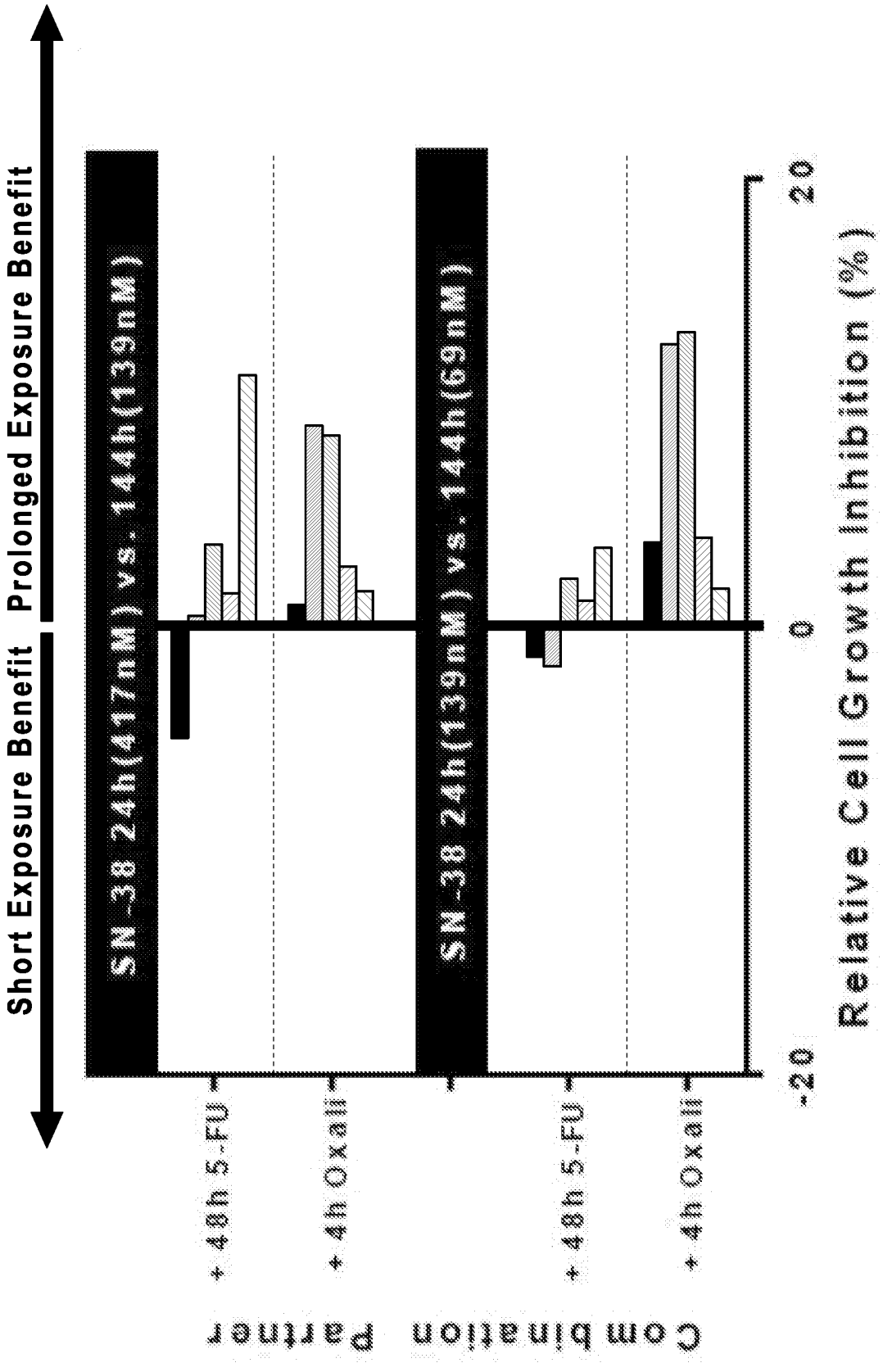

Short Exposure Benefit
Prolonged Exposure Benefit
SN-38 24h(417nM) vs. 144h(139nM)
SN-38 24h(139nM) vs. 144h(69nM)
+ 48h 5-FU
+ 4h Oxali
+ 48h 5-FU
+ 4h Oxali
Combination Partner
-20
0
20
Relative Cell Growth Inhibition (%)

FIG. 1D

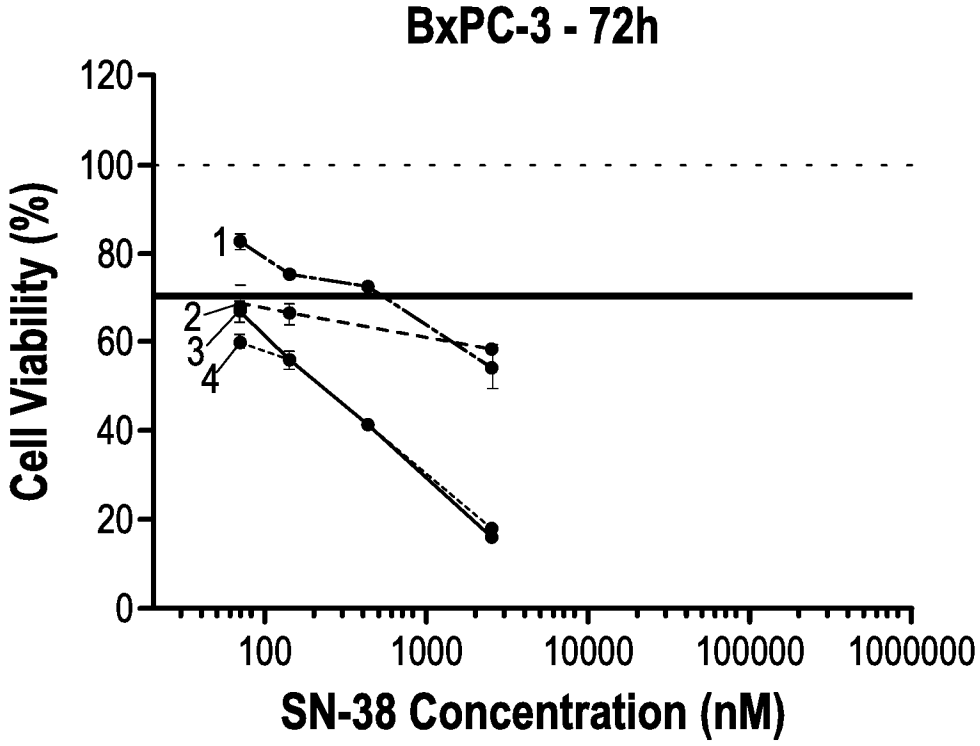


FIG. 2A

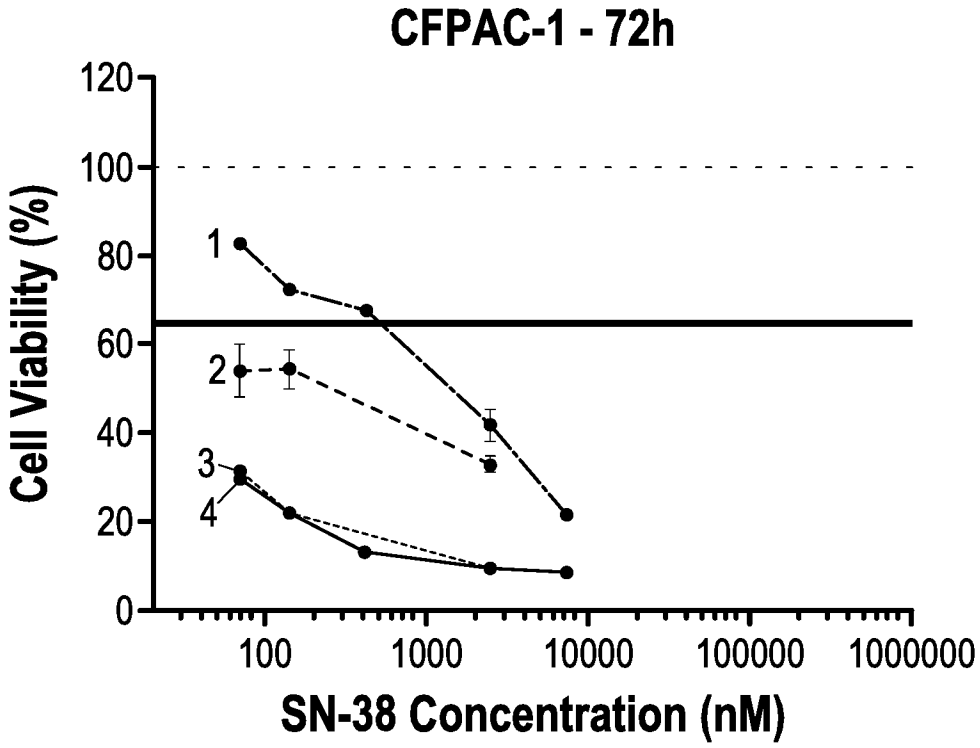


FIG. 2B

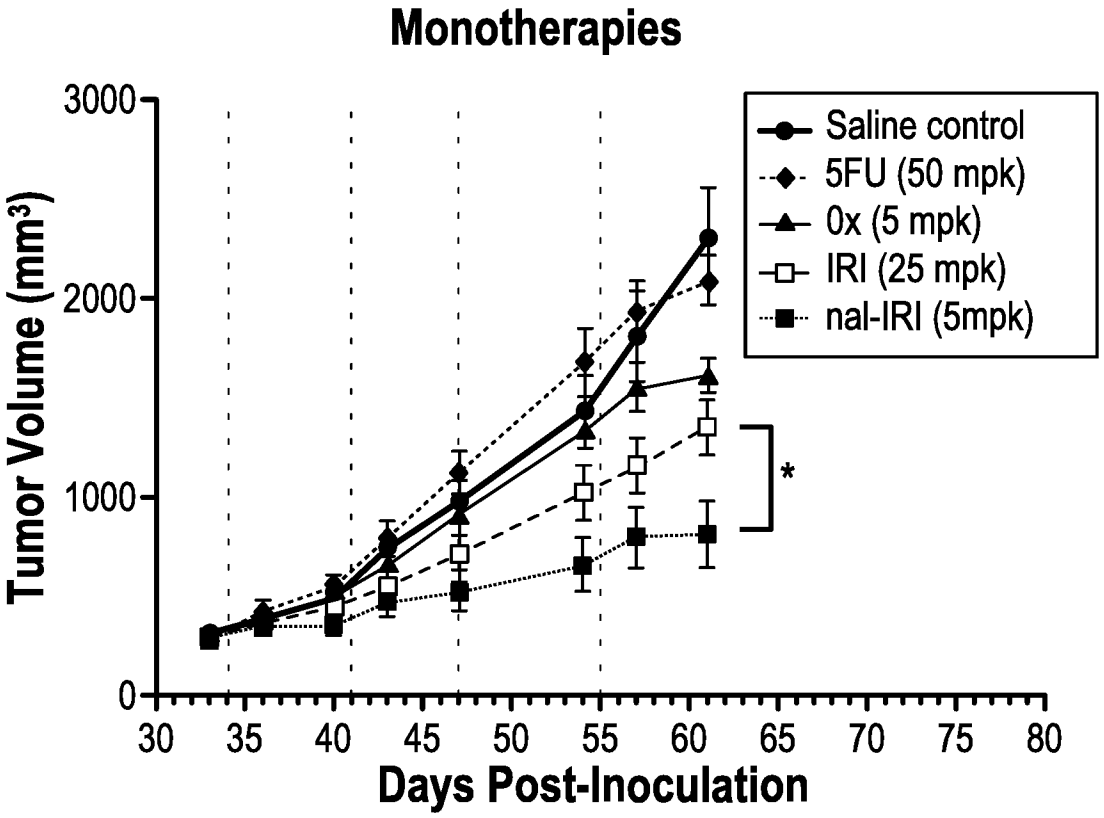


FIG. 3A

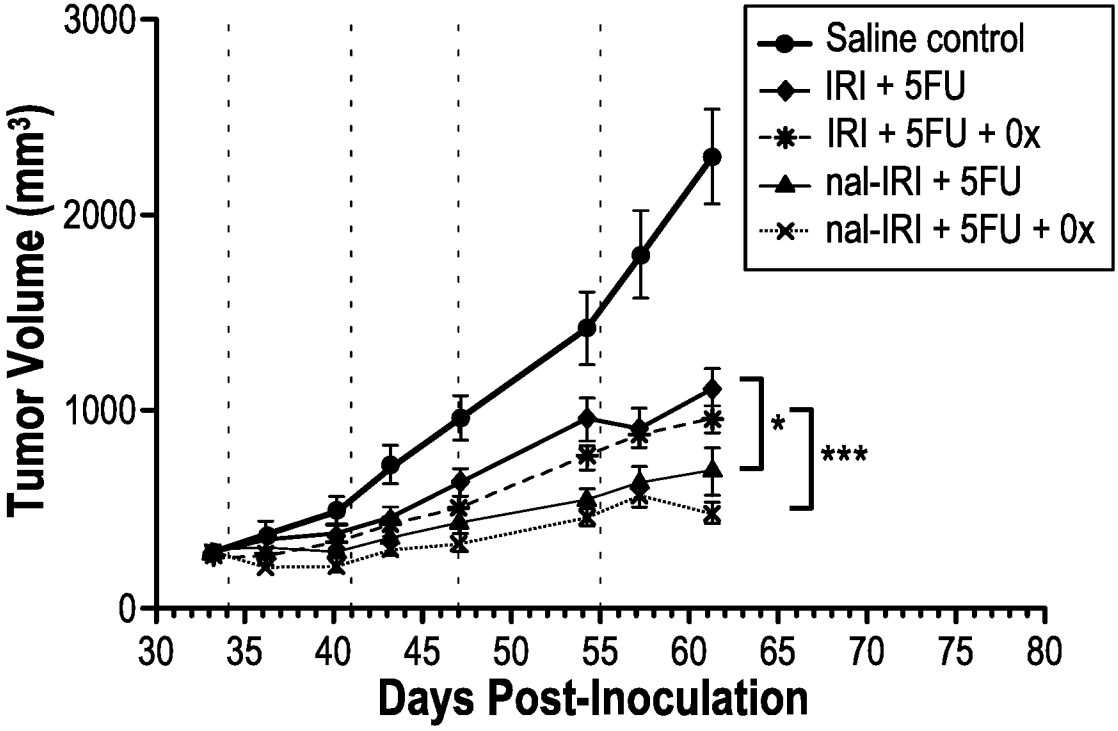


FIG. 3B

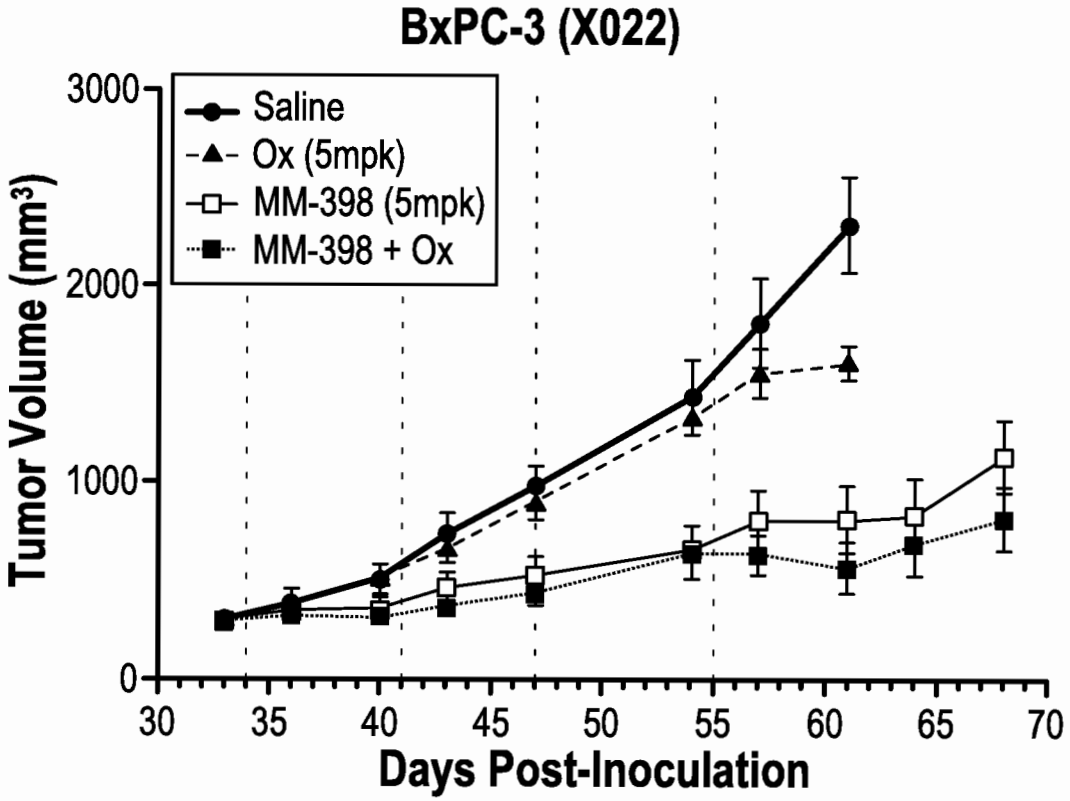


FIG. 4A

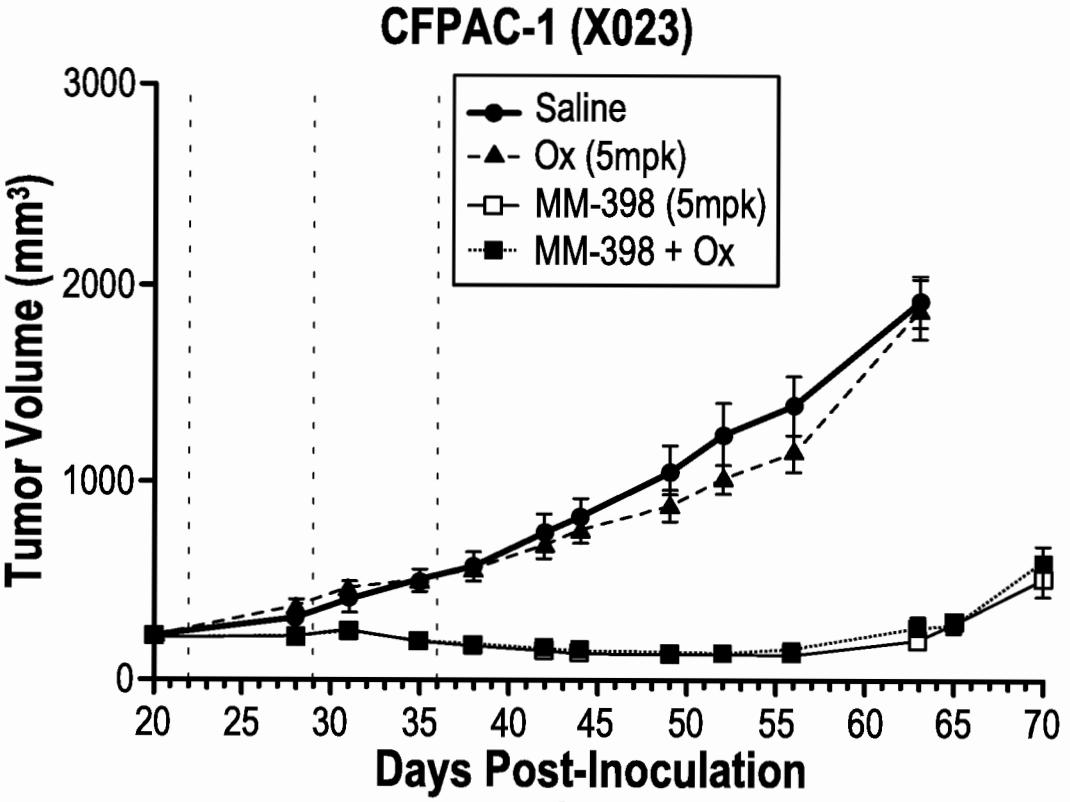


FIG. 4B

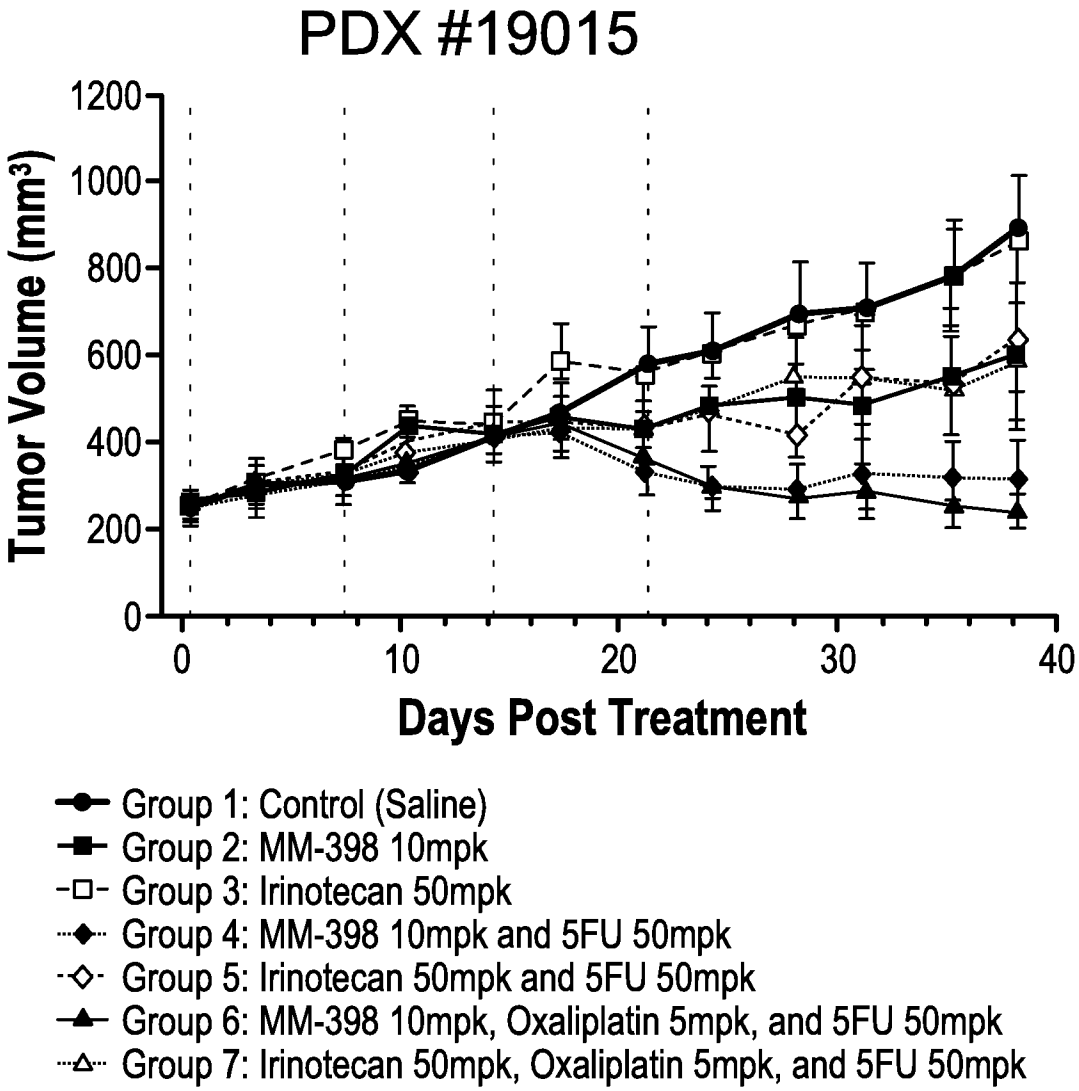

PDX #19015
Tumor Volume (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
Days Post Treatment
Group 1: Control (Saline)
Group 2: MM-398 10mpk
Group 3: Irinotecan 50mpk
Group 4: MM-398 10mpk and 5FU 50mpk
Group 5: Irinotecan 50mpk and 5FU 50mpk
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk
Group 7: Irinotecan 50mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5A

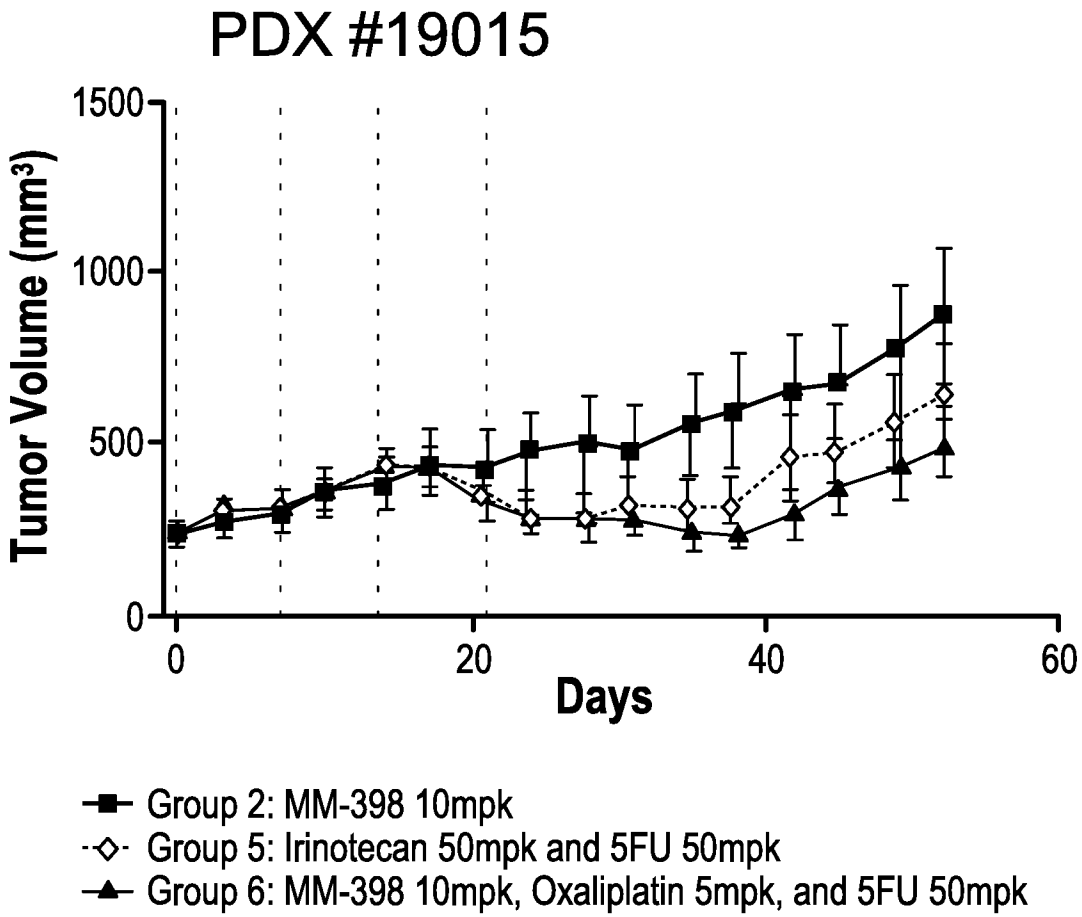


FIG. 5B

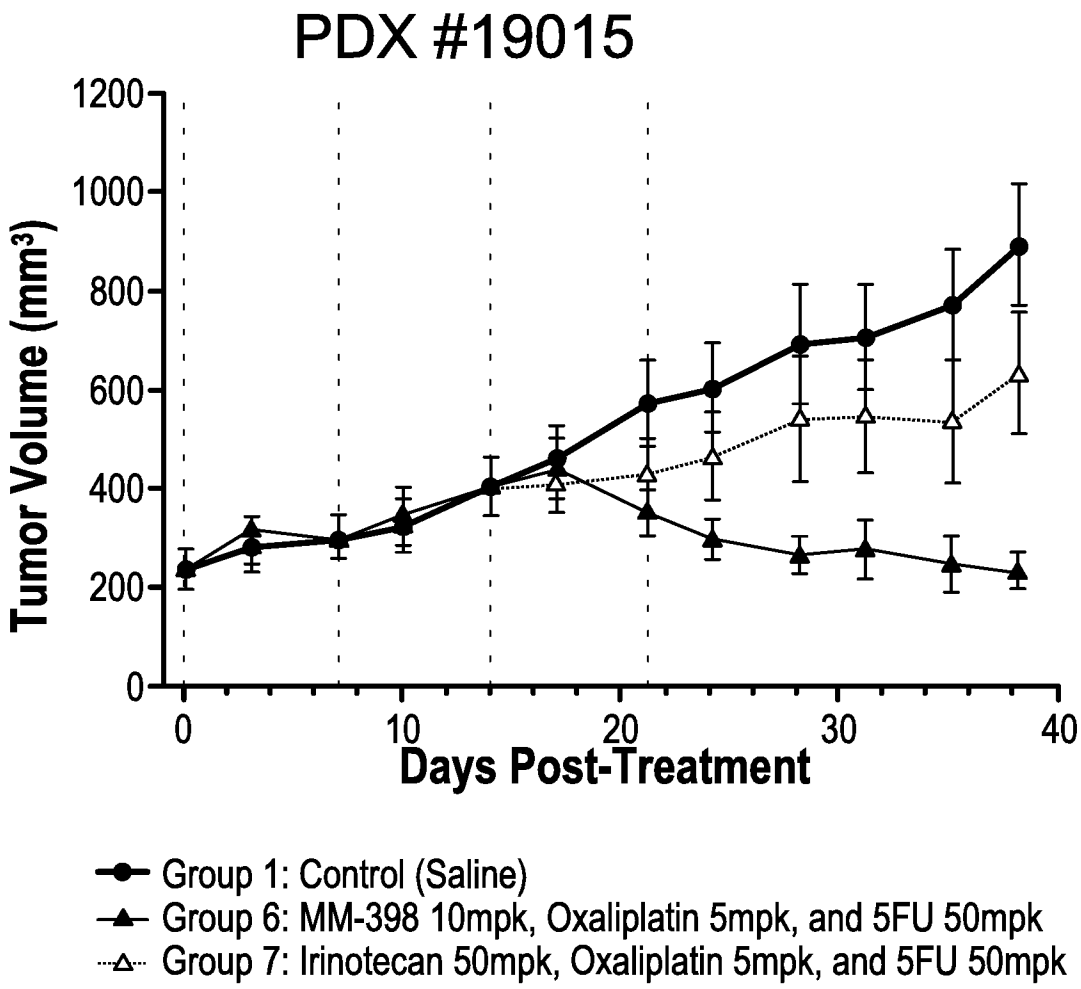


FIG. 5C

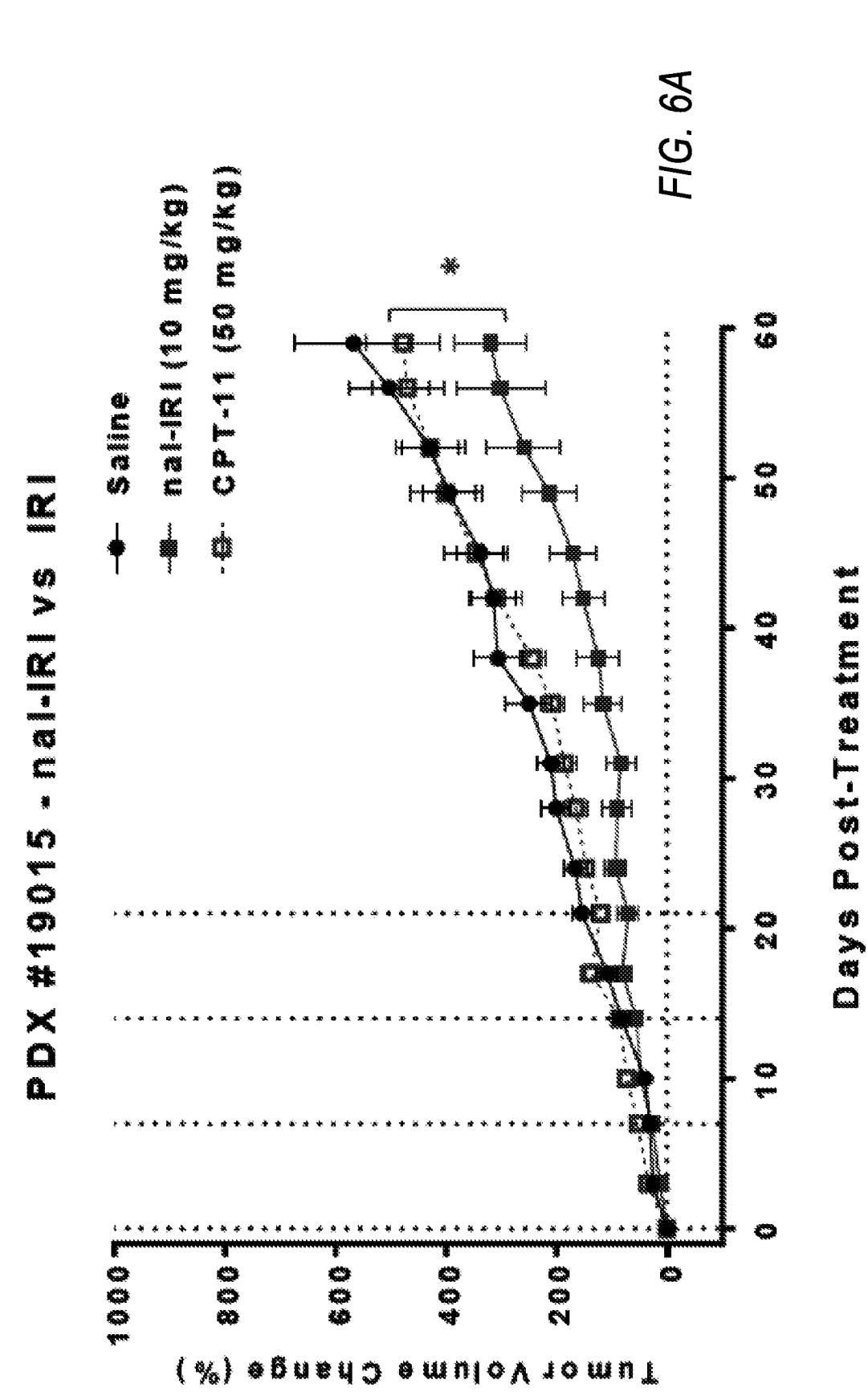

PDX #19015 - nal-IRI vs IRI
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6A

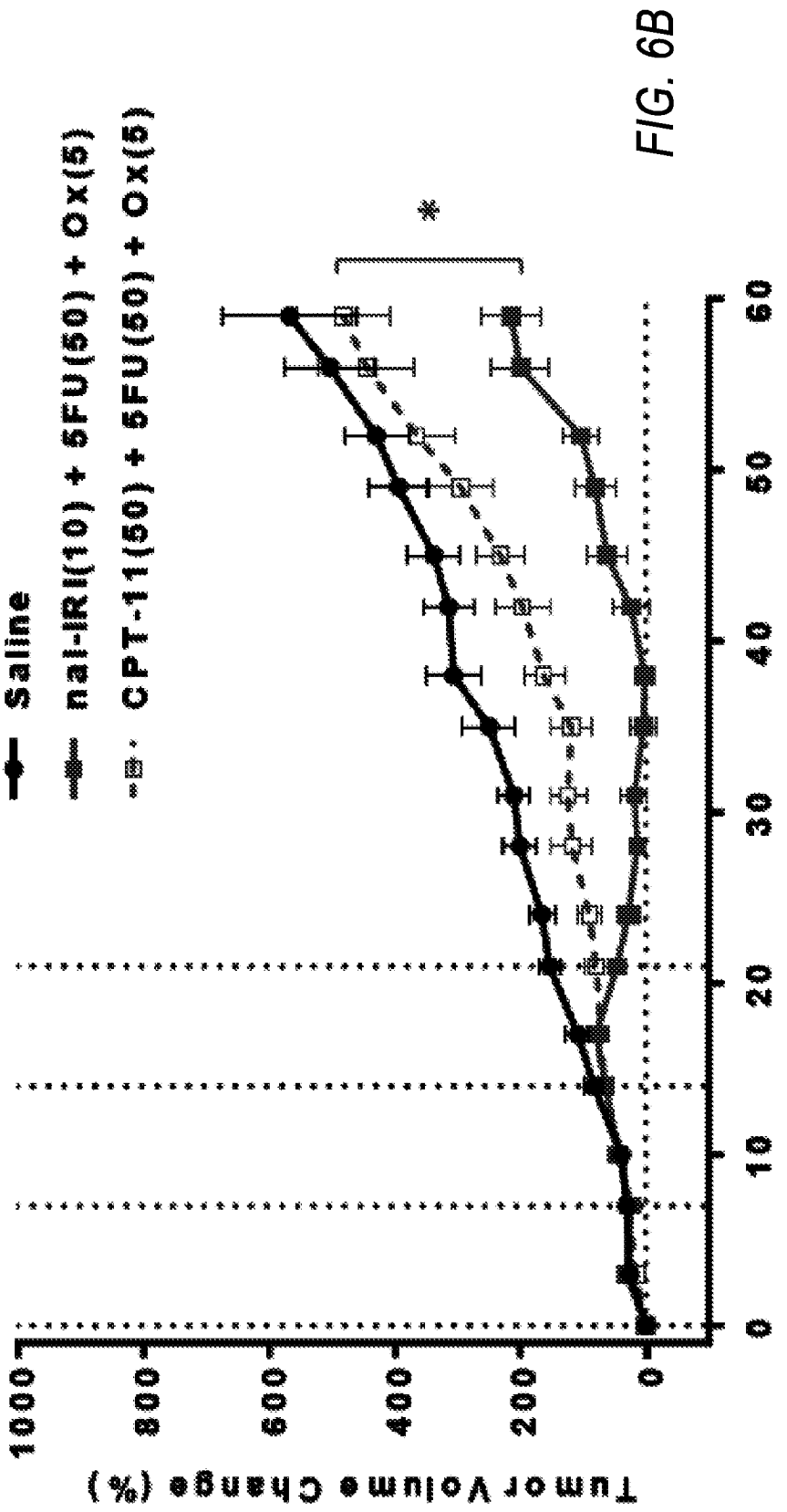

PDX #19015 - Combinations
Saline
nal-IRI(10) + 5FU(50) + Ox(5)
CPT-11(50) + 5FU(50) + Ox(5)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6B

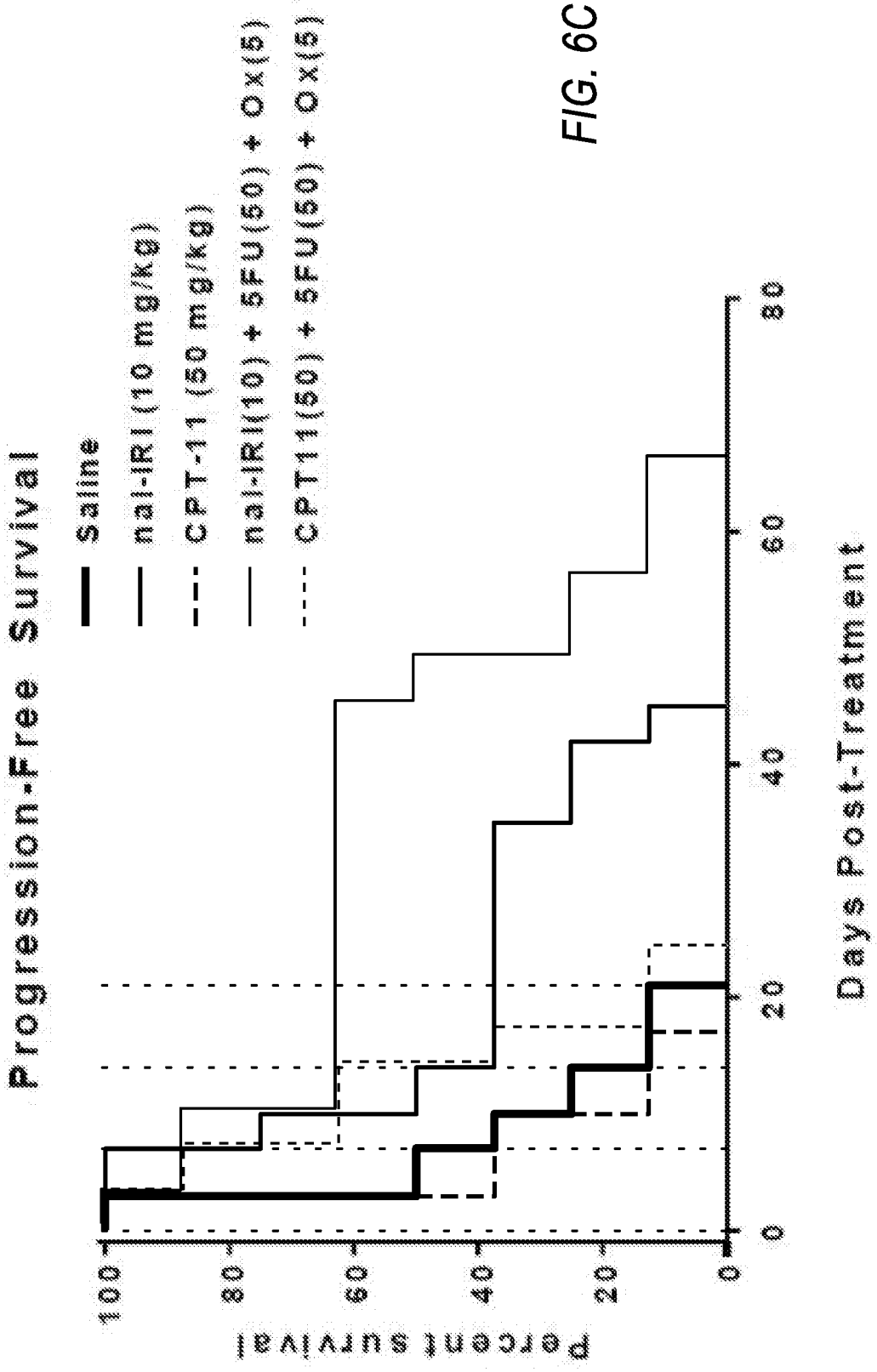


FIG. 6C

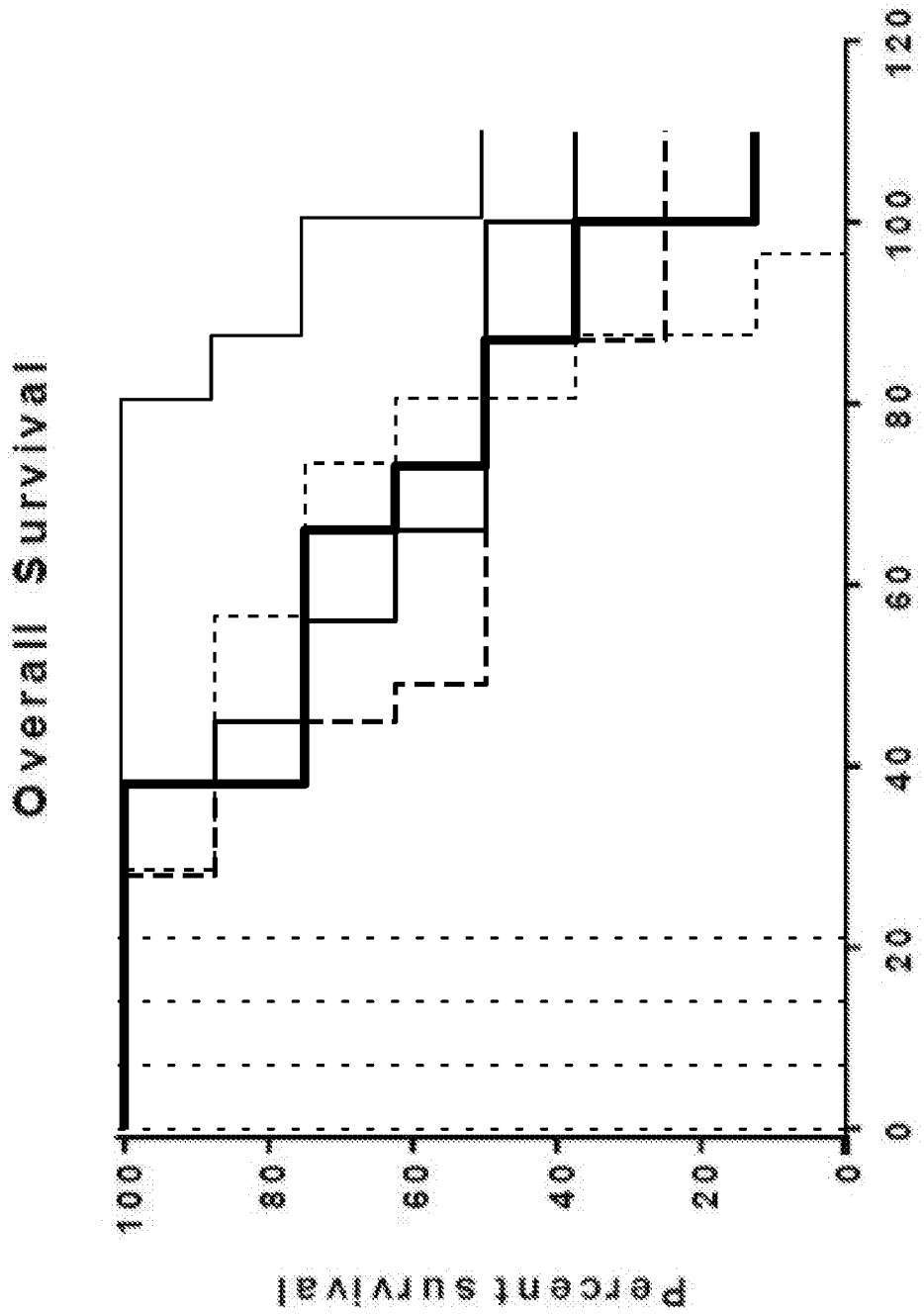

Overall Survival
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
120
Days Post-Treatment

FIG. 6D

G1 – Control
G2 – MM-398 10 mpk
G3 – Irinotecan 50 mg/kg
G4 – MM-398 10 mpk + 5FU 50 mpk
G5 – Irinotecan 50 mpk + 5FU 50 mpk
G6 – MM-398 10 mpk + 5FU 50 mpk + Ox 5 mpk
G7 – Irinotecan 50 mpk + 5FU 50 mpk + Ox 5 mpk

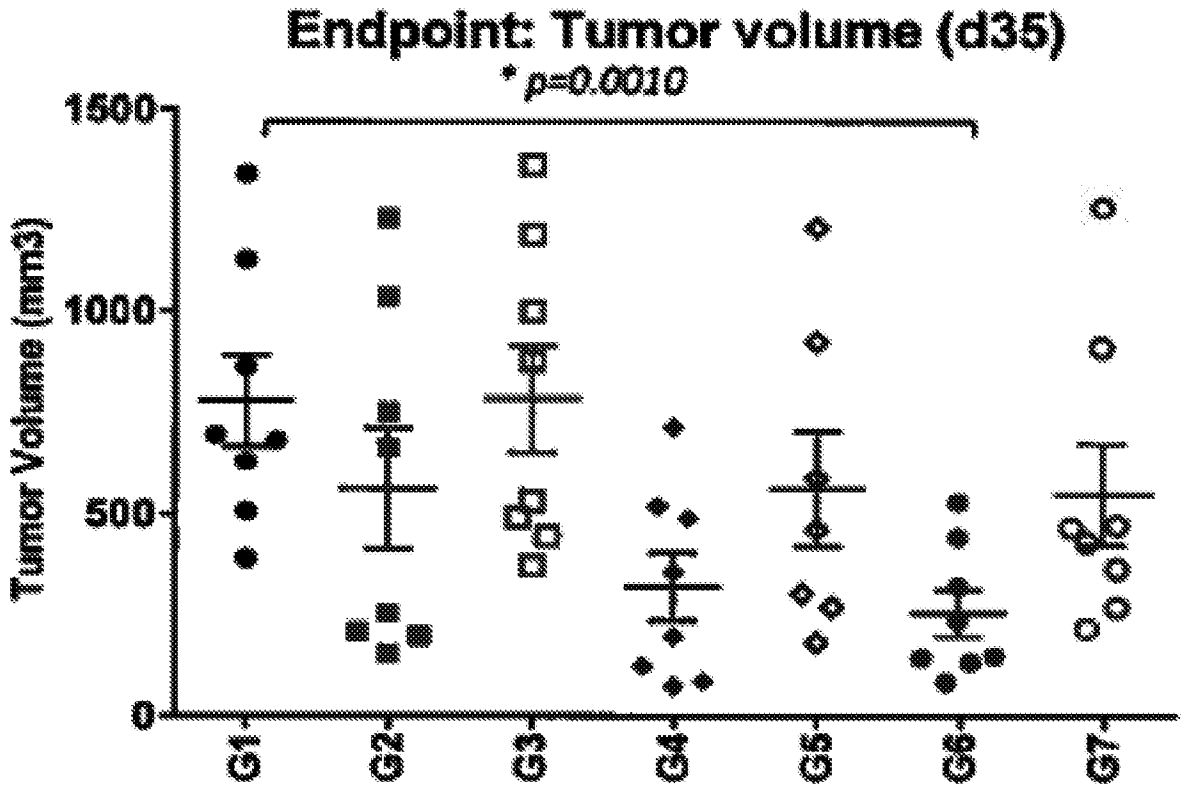


FIG. 7

	Control	MM-398	IRI	NAPOLI	FOLFIRI	NAPOX	FOLFIRINOX
Tumor Vol (mean mm^3,d35)	779	562	753	321	523	255	445
TGI (% at d35)	n/a	27.9%	3.4%	58.8%	32.9%	67.3%	42.9%
Median Days to $1000mm^3$	50.5 (n=8 of 8)	68 (6 of 8, 2 est)	43.5 (8 of 8)	70 (6 of 8, 2 est)	56 (7 of 7)	77 (8 of 8)	56 (8 of 8)
Stable Disease (-30% - +30%)	0	3	1	2	3	2	4
PR (30%-95% reduction)	0	0	0	3	0	4	0
CR (≥95% reduction)	0	0	0	0	0	0	0
Response Rate (≥30% reduction)	0%	0%	0%	38%	0%	50%	0%
Disease Control	0%	38%	13%	63%	38%	75%	50%
Rate (ORR + SD)							
Median Progression Free Survival (days)	5	12	3	36.5	10	47	14
Median OS(days)	80	83	68	100	80	105	80

FIG. 8

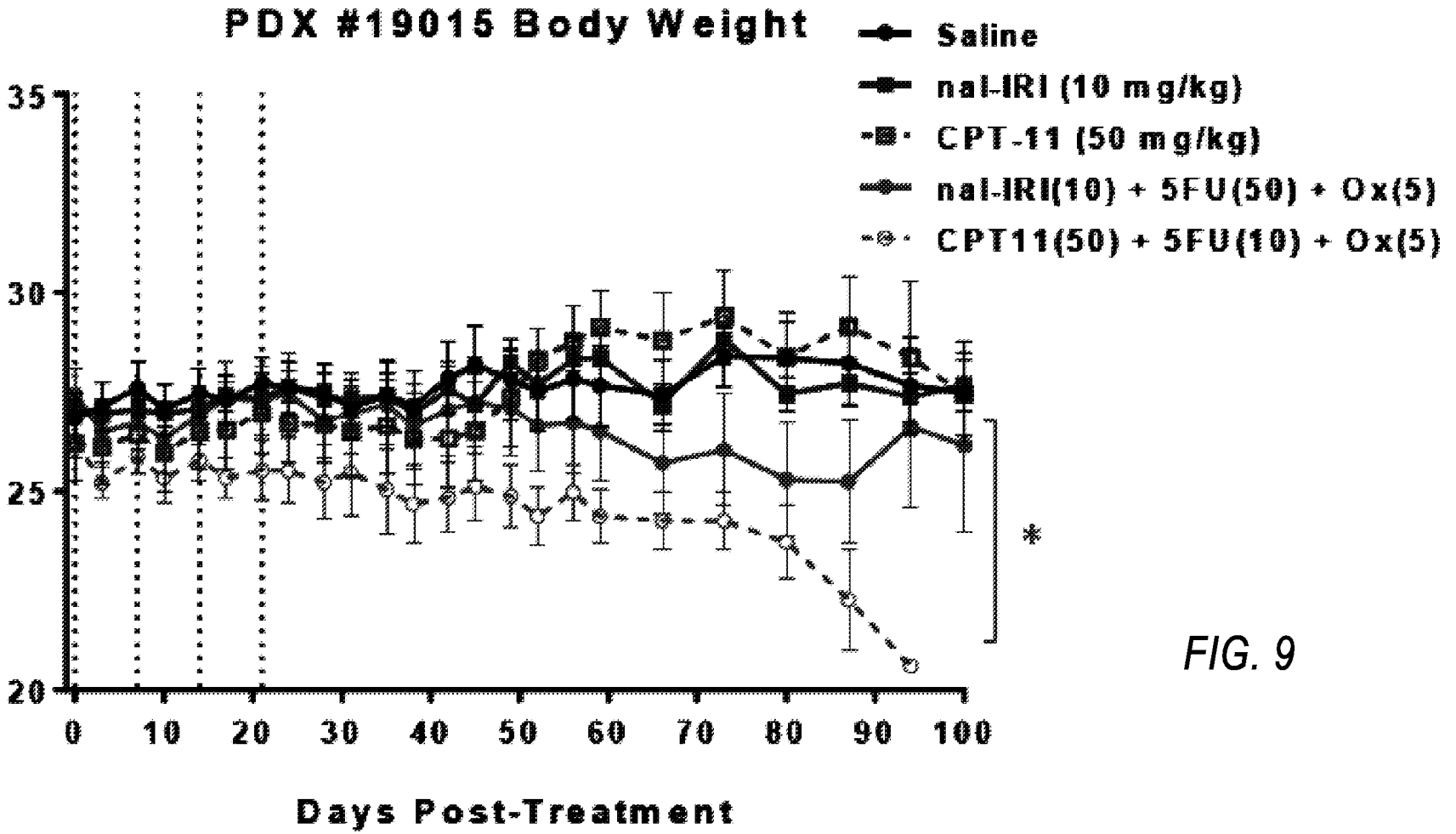


FIG. 9

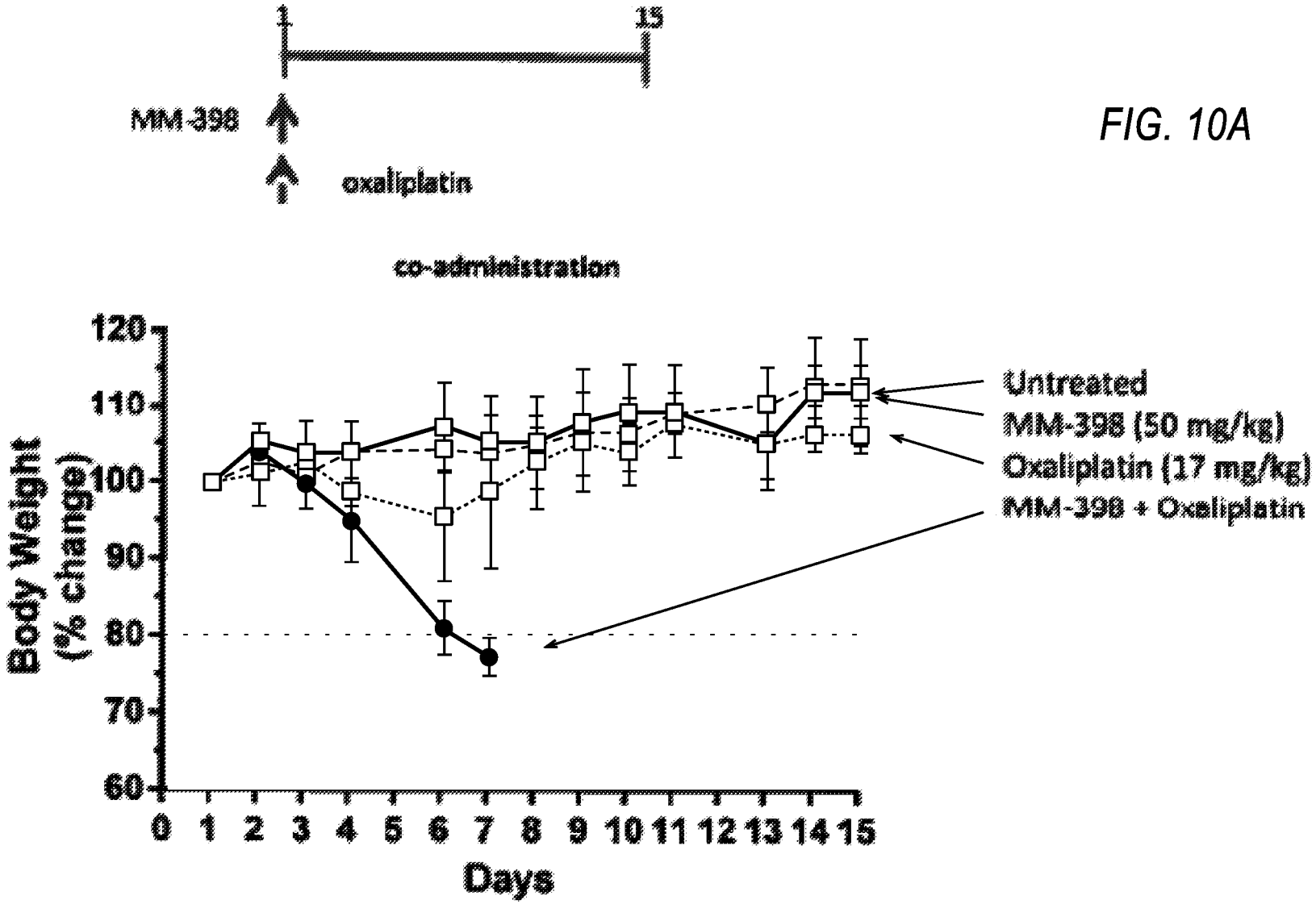


FIG. 10A

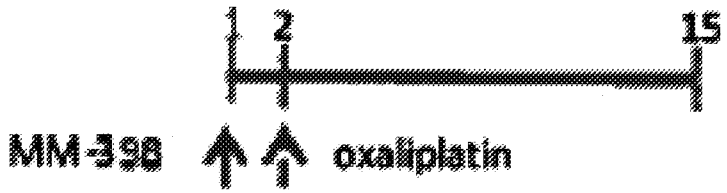
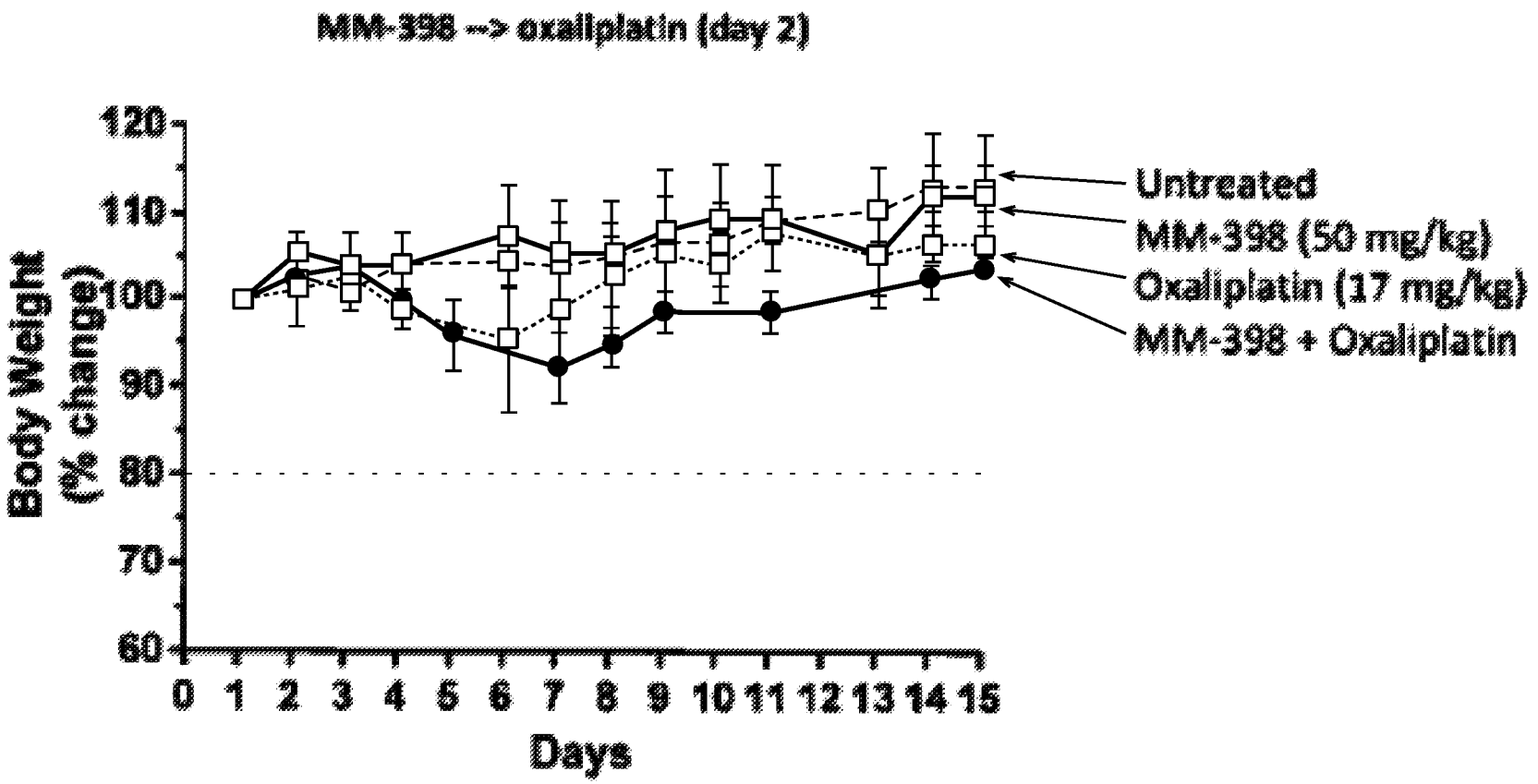


FIG. 10B



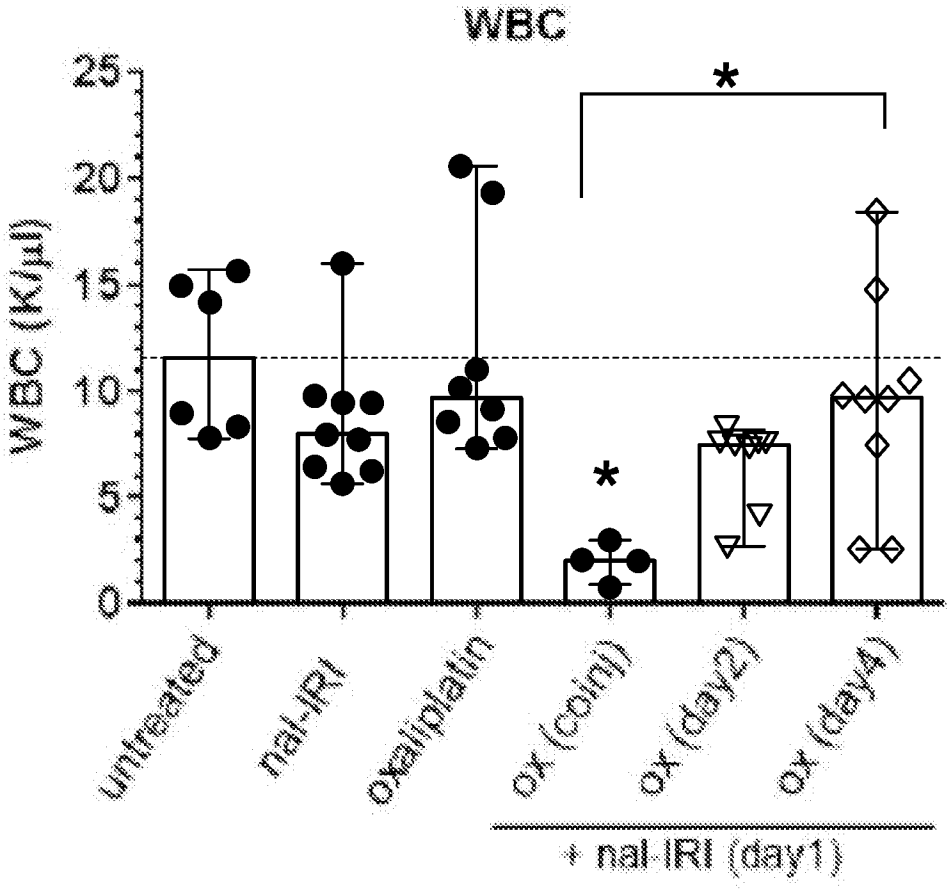


FIG. 11A

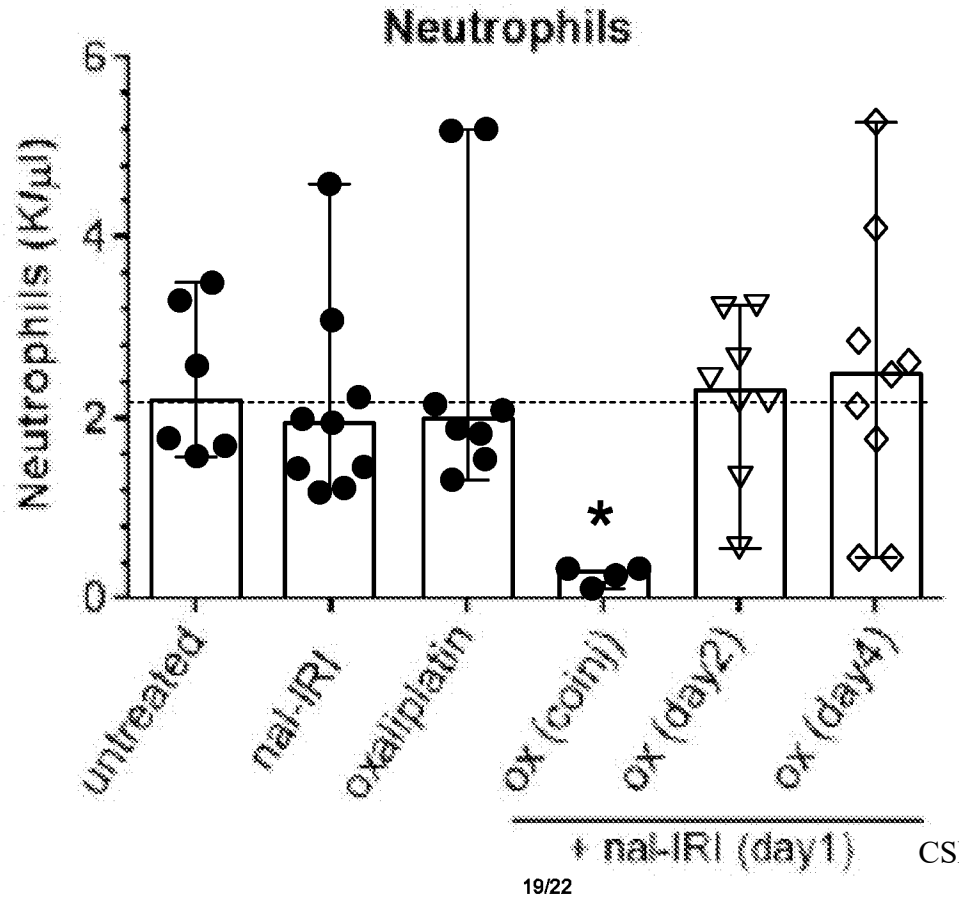


FIG. 11B

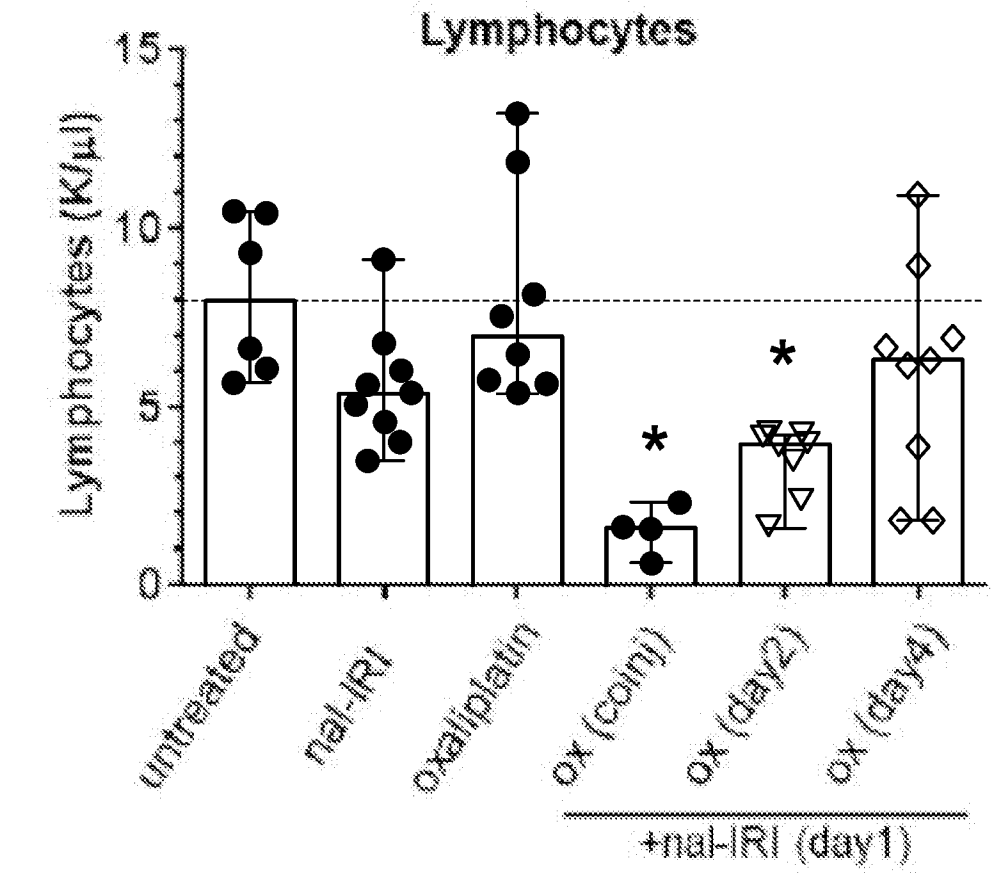


FIG. 11C

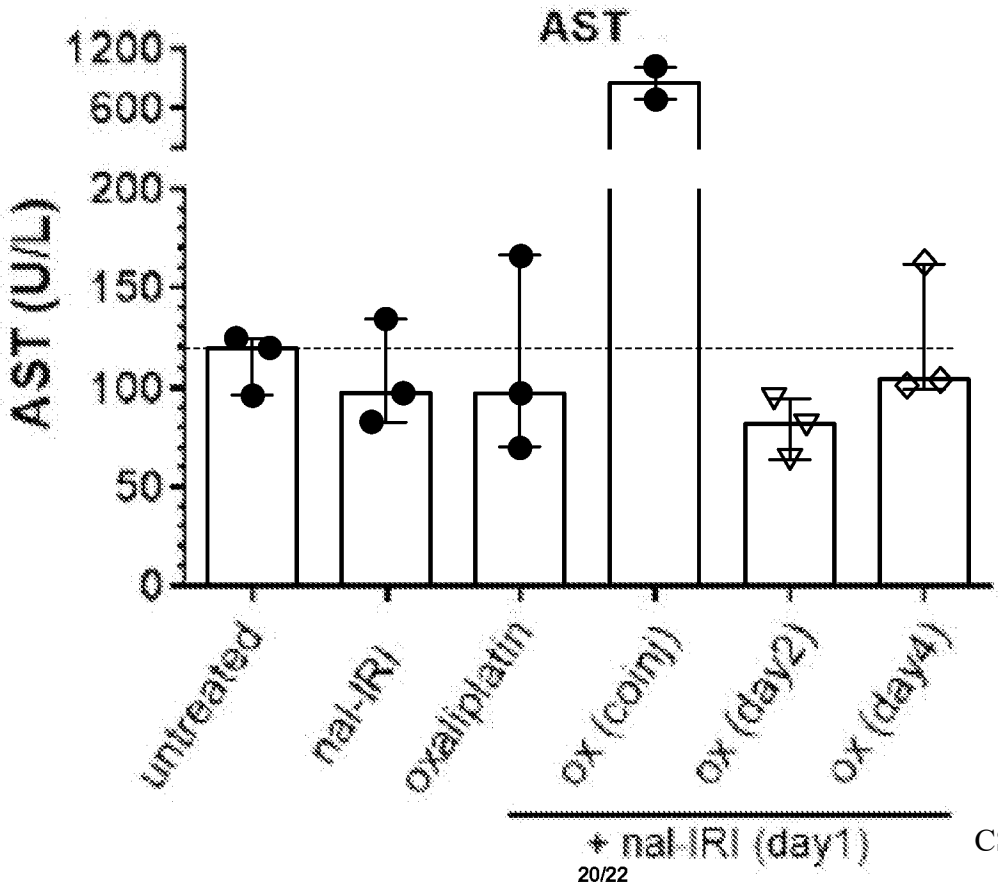


FIG. 11D

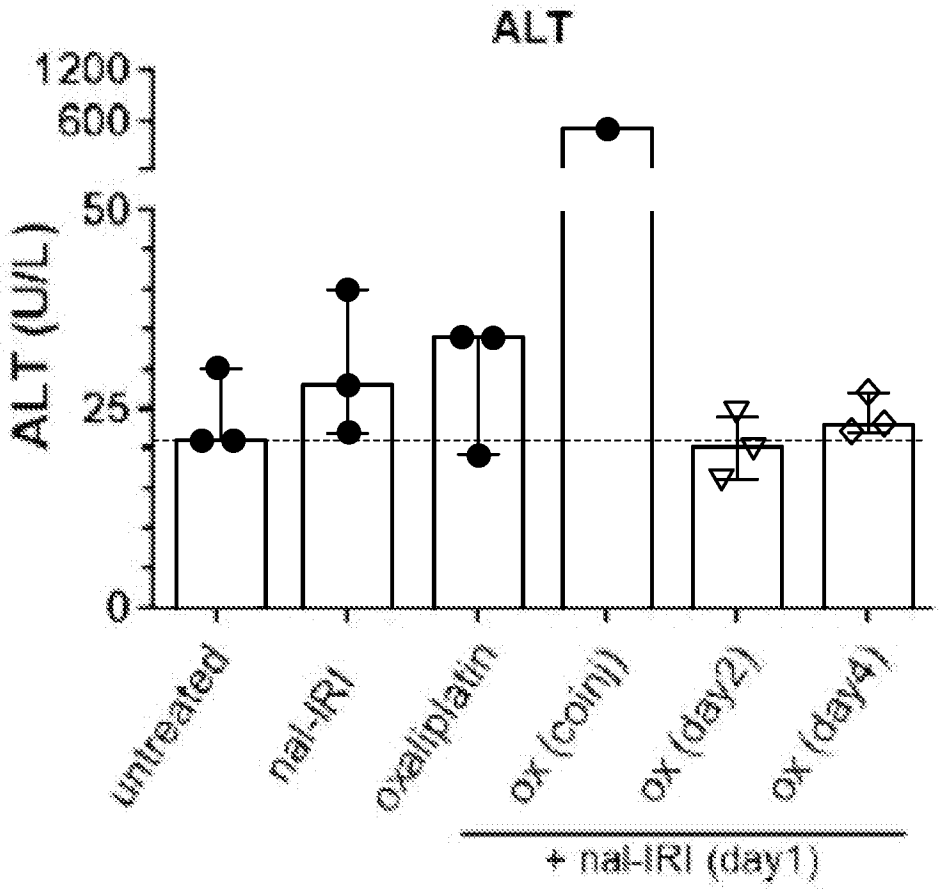


FIG. 11E

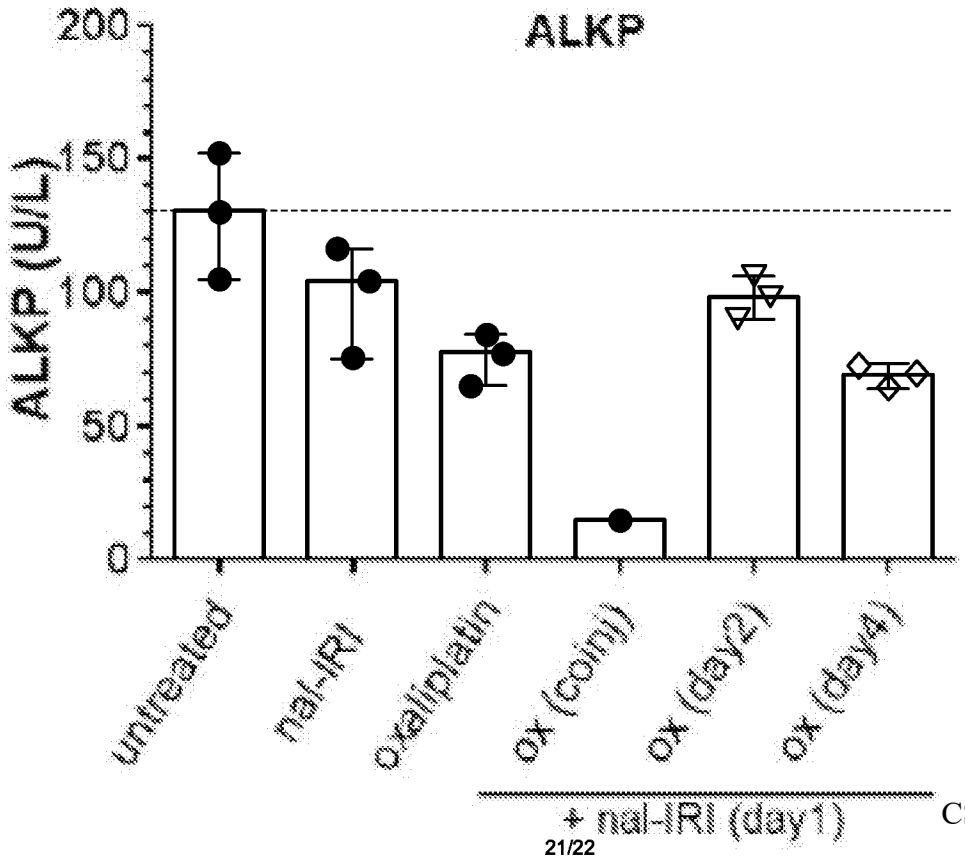


FIG. 11F

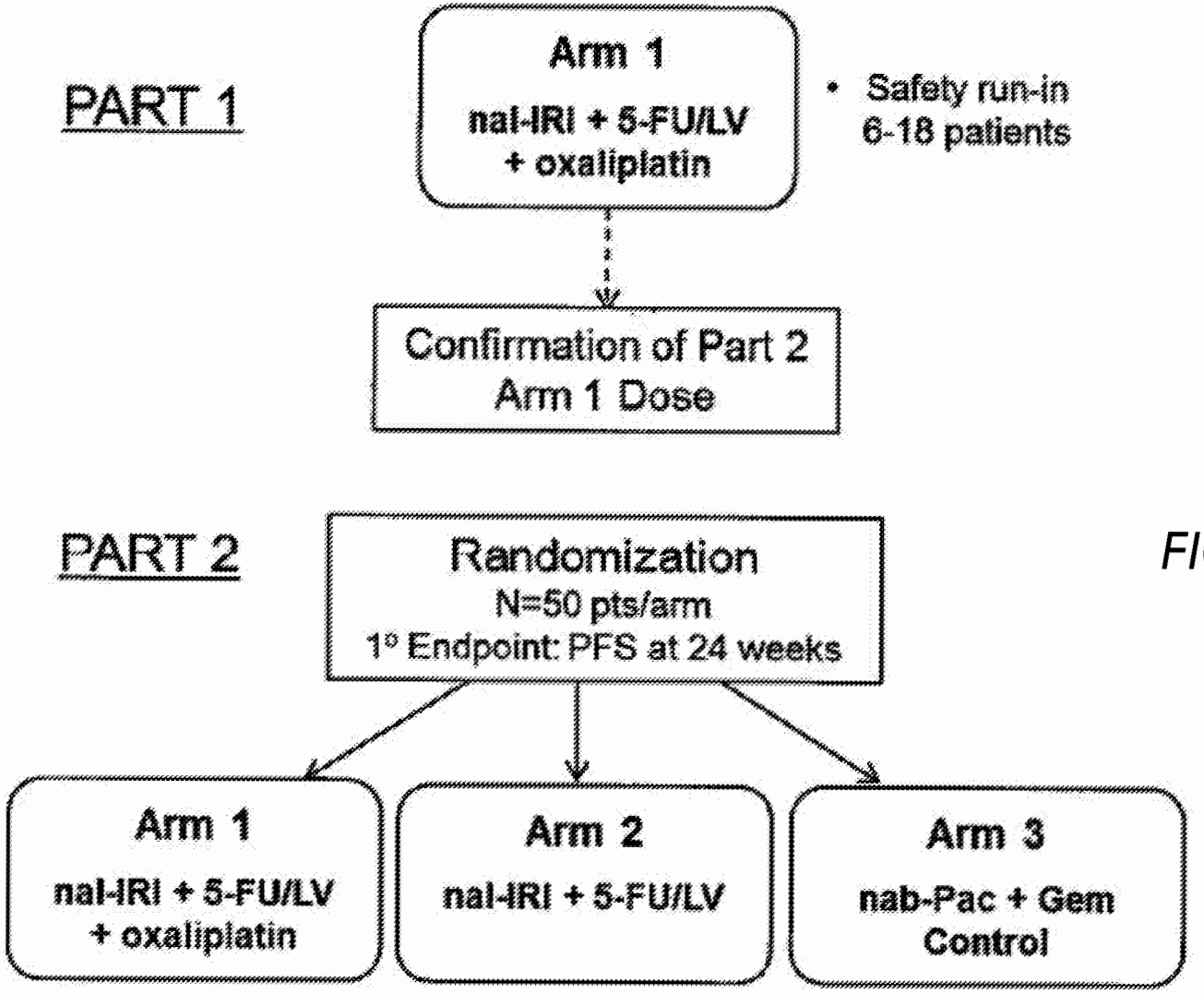


FIG. 12

Abstract

Combination therapy regimens including liposomal irinotecan, oxaliplatin and 5-fluorouracil are useful in the treatment of pancreatic cancer, including treatment of patients diagnosed with previously untreated metastatic adenocarcinoma of the pancreas. The combination therapy can include the administration of liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil once every two weeks.

Claims

1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 or 85 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.
2. The method of claim 1, wherein a total of 60 mg/m^2 oxaliplatin is administered to the patient during the antineoplastic therapy once every two weeks.
3. The method of claim 1, wherein a total of 85 mg/m^2 oxaliplatin is administered to the patient during the antineoplastic therapy once every two weeks.
4. The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.
5. The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.
6. The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.
7. The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.
8. The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.
9. The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.
11. The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
12. The method of claim 2, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes, and the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
13. The method of claim 12, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to the leucovorin; the leucovorin is administered immediately prior to each administration of the 5-fluorouracil and each administration of 5-fluorouracil is administered as an infusion over 46 hours.
14. The method of claim 3, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes, and the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
15. The method of claim 14, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to the leucovorin; the leucovorin is administered immediately prior to each administration of the 5-fluorouracil and each administration of 5-fluorouracil is administered as an infusion over 46 hours.
16. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the

patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

a. 60 mg/m^2 of liposomal irinotecan,

b. 85 mg/m^2 oxaliplatin,

c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

17. The method of claim 16, wherein

a. the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated liposome vesicles comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE);

b. the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle;

c. each administration of the liposomal irinotecan is administered prior to the leucovorin;

d. the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and

e. each administration of 5-fluorouracil is administered as an infusion over 46 hours.

18. The method of claim 17, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and anti-emetic to the patient prior to the antineoplastic therapy.

19. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the

patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 60 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

20. The method of claim 19, wherein

a. the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated liposome vesicles comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE);
b. the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle;
c. each administration of the liposomal irinotecan is administered prior to the leucovorin;
d. the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and
e. each administration of 5-fluorouracil is administered as an infusion over 46 hours.

METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 15/241,106, filed August 19, 2016, which claims the benefit of priority to U.S. Provisional Application Nos. 62/208,209, filed August 21, 2015, 62/216,736, filed September 10, 2015, 62/273,244, filed December 30, 2015, 62/281,473, filed January 21, 2016, 62/302,341, filed March 2, 2016, 62/323,245, filed April 15, 2016 and 62/343,313, filed May 31, 2016. The entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to novel therapies useful in the treatment of pancreatic cancer, including the use of liposomal irinotecan in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer.

BACKGROUND

Pancreatic cancer is chemotherapy-resistant, with an extremely poor prognosis. It is the fourth leading cause of cancer death in the United States; the 5-year survival rate is 6%. The incidence of pancreatic cancer has increased during the past several decades and in 2014, an estimated 46,420 patients were diagnosed with pancreatic cancer and 39,590 died. Pancreatic cancer is projected to surpass liver, breast, prostate, and colorectal cancers to become the second-leading cause of cancer-related death by 2030. These statistics reflect the dire nature of the disease and lack of effective therapies. The location of the tumor results in few early symptoms and is often diagnosed at a late stage as a result. The absence of effective screening tools, and a limited understanding of risk factors, means that patients have advanced or metastatic disease at the time of diagnosis. Given the poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, new treatment options are still needed.

Tolerability of multi-drug regimens is important in cancer treatment. The longer the duration of

manageable treatment should translate into improved outcome due to longer drug exposure. During the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX). However, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status (i.e. ECOG performance score of 0 or 1). With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity. Therefore, if equally effective double regimens can be identified, patients may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit. Although the FOLFIRINOX regimen has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011, there are some concerns about the toxicity associated with FOLFIRINOX. One dose regimen of FOLFIRINOX is 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, and fluorouracil at a dose of 400 mg/m^2 administered by IV bolus followed by a continuous infusion of 2400 mg/m^2. Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules.

CPT-11 is irinotecan hydrochloride trihydrate, marketed as Camptosar® in the United States. MM-398 is a liposomal irinotecan and is marketed in the U.S. as the FDA-approved product ONIVYDE® in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

SUMMARY

Improved antineoplastic therapies for the treatment of pancreatic cancer provide the administration of liposomal irinotecan in combination with oxaliplatin and 5-fluorouracil to patients with previously untreated pancreatic cancer (e.g., untreated metastatic pancreatic adenocarcinoma, or mPAC). The 5-fluorouracil can be administered in combination with

leucovorin. The improved antineoplastic therapies can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens.

A method of treating pancreatic cancer can comprise the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient. Optionally, leucovorin can also be administered prior to each administration of the 5-fluorouracil. Each administration of the liposomal irinotecan can be administered in a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein). A total of 2,400 mg/m^2 5-fluorouracil can be administered over 46 hours starting on each day when the liposomal irinotecan is administered. A total of 60, 75 or 85 mg/m^2 oxaliplatin can be administered on each day the liposomal irinotecan is administered. A total of 200 mg/m^2 (l) leucovorin can be administered prior to each administration of the 5-flurouracil (e.g., optionally administered as 400 mg/m^2 of (l+d) leucovorin). The antineoplastic therapy can be administered starting on days 1 and 15 of a 28-day treatment cycle, with the liposomal irinotecan, oxaliplatin, and optionally leucovorin administered on days 1 and 15 and initiating the 46-hour administration of the 5-fluorouracil on days 1 and 15.

The invention is based in part on several pre-clinical discoveries. First, liposomal irinotecan improved anti-tumor activity of the topoisomerase 1 inhibitor SN-38 (an active metabolite of irinotecan) relative to exposure-matched doses of non-liposomal irinotecan. Second, liposomal irinotecan combined with 5-fluorouracil and oxaliplatin consistently improved tumor growth inhibition and survival in mouse xenograft models of pancreatic cancer relative to non-liposomal irinotecan, without exacerbating the baseline toxicities of these agents.

In addition, the invention is based in part on the discovery that the administration of a dose of 80 mg/m^2 liposomal irinotecan was not well tolerated in humans when administered in combination with 60 mg/m^2 oxaliplatin, 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 (l+d) leucovorin. Accordingly, preferred methods of treating (previously untreated) pancreatic cancer provide for the administration of a human-tolerated antineoplastic therapy once every two weeks, where each administration of the antineoplastic therapy is a combination of the

antineoplastic agents liposomal irinotecan, oxaliplatin and 5-fluorouracil provided herein. Preferably, the antineoplastic therapy administered once every two weeks consists of: (a) a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein), (b) a total dose of 60-85 mg/m^2 oxaliplatin (including, e.g., 60 or 85 mg/m^2), and (c) a total of 2,400 mg/m^2 5-fluorouracil optionally administered in combination with leucovorin. Optionally, the combination can include administration of a total of 200 mg/m^2 (l) leucovorin (optionally administered as 400 mg/m^2 of (l+d) leucovorin), prior to initiating the administration of the 5-fluorouracil. Preferably, no other antineoplastic agent is administered during the antineoplastic therapy, other than amounts of SN-38 produced within the patient from the liposomal irinotecan, after administration of the liposomal irinotecan. For example, the antineoplastic therapy can be administered without (non-liposomal) CPT-11 irinotecan. Preferably, the liposomal irinotecan, oxaliplatin, and (optionally) leucovorin are consecutively administered as separate infusions on a single (first) day and the 5-fluorouracil is administered starting on the first day after the administration of the leucovorin (if administered) and continuing into the following day (e.g., over a total of 46 hours).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a graph showing the simulated levels of the active irinotecan metabolite SN-38 over time based on liposomal irinotecan human clinical biopsy data and human clinical trial data.

Figure 1B is a schematic showing how the tumor exposure of SN-38 over time observed with liposomal irinotecan (MM-398) is prolonged compared to SN-38 tumor exposure from non-liposomal irinotecan (CPT-11).

Figure 1C is a graph showing the percent relative cell growth inhibition of SN-38 based on various times of total SN-38 cell exposure for 5 different cell lines.

Figure 1D is a graph showing the percent relative cell growth inhibition of the cell lines tested in Figure 1C at different exposure times (4 hours or 48 hours) for different combinations of SN-38 with 5-fluorouracil (5-FU) or oxaliplatin (oxali).

Figure 2A is a graph showing the cell viability as a function of SN-38 exposure for BxPC-3 pancreatic cancer cells.

Figure 2B is a graph showing the cell viability as a function of SN-38 exposure for CFPAC-1 pancreatic cancer cells.

Figure 3A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with individual antineoplastic agents: including 5-fluorouracil (5FU), oxaliplatin (Ox), (non-liposomal) irinotecan (IRI) and MM-398 liposomal irinotecan (nal-IRI).

Figure 3B is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with various combinations of antineoplastic agents: (non-liposomal) irinotecan (IRI) and 5FU; (non-liposomal)irinotecan (IRI), oxaliplatin and 5FU; MM-398 liposomal irinotecan (nal-IRI) and 5FU; and 398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU.

Figure 4A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 4B is a graph showing the tumor volume over time measured in a CFPAC-1 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 5A is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5B is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the MM-398 containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU), MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5C is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the oxaliplatin containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6A is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (nal-IRI) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan).

Figure 6B is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6C is a graph of the progression free survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6D is a graph of the overall survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 7 is a graph showing the tumor volume measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 8 is a table showing the results obtained from a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan alone, non-liposomal irinotecan alone (monotherapy), MM-398 liposomal irinotecan in combination with 5FU (NAPOLI, double therapy), MM-398 liposomal irinotecan in combination with 5FU + oxaliplatin (NAPOX, triple therapy) and non-liposomal irinotecan combined with oxaliplatin and 5-fluorouracil (FOLFIRINOX).

Figure 9 is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of a saline control, liposomal irinotecan (nal-IRI), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin on days 0, 7, 14 and 21.

Figure 10A is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given together on the same day.

Figure 10B is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given sequentially on separate successive days with the MM-398 administered on day 1 and the oxaliplatin administered on day 2.

Figures 11A, 11B and 11C are bar graphs depicting hematological toxicities observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin

administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: A. White blood cells; B. Neutrophils; and C. Lymphocytes.

Figures 11D, 11E and 11F is bar graphs depicting liver enzyme levels observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: D. aspartate aminotransferase (AST); E. alanine transaminase (ALT); F. alkaline phosphatase (ALKP).

Figure 12 is a schematic of methods of treating pancreatic cancer, including methods comprising the administration of liposomal irinotecan, oxalipaltin, 5-fluorouracil and leucovorin.

DETAILED DESCRIPTION

Unless otherwise indicated, the dose of liposomal irinotecan or irinotecan liposome as recited herein refers to the amount of irinotecan hydrochloride trihydrate providing an amount of irinotecan encapsulated in the liposome of the liposomal irinotecan or irinotecan liposome. For example, a dose of 60 mg/m^2 liposomal irinotecan refers to an amount of the liposomal irinotecan providing the same amount of liposome encapsulated irinotecan that is present in 60 mg/m^2 of irinotecan hydrochloride trihydrate, and is equivalent to a dose of about 50 mg/m^2 of liposomal irinotecan based on the amount of the irinotecan free base encapsulated in the liposomal irinotecan.

As used herein, unless otherwise indicated, the term "nal-IRI" (nanoliposomal irinotecan) and "MM-398" refer to a form of liposomal irinotecan. The term "CPT-11" refers to (non-liposomal) irinotecan hydrochloride trihydrate.

As used herein, "5-FU" and "5FU" and used interchangeably and refer to 5-fluorouracil.

All cited documents are incorporated herein by reference.

Using pancreatic cancer cell lines (Example 1), we demonstrated enhanced cell death when liposomal irinotecan treatment is simulated using prolonged exposure of SN-38 (the active

metabolite of irinotecan) in combination with 5-FU and oxaliplatin. Figure 1 shows that prolonged exposure of SN-38 simulates MM-398 treatment in vitro. Referring to Figure 1A, MM-398 treatment results in prolonged tumor exposure to the active metabolite, SN-38, compared to non-liposomal irinotecan (CPT-11). Referring to Figure 1B, prolonged low-dose exposure of SN-38 mimics MM-398 tumor delivery in vitro. Referring to Figure 1C, prolonged low-dose exposure resulted in greater cell growth inhibition in multiple pancreatic cancer cell lines. The graph comprises four sections, and for each section the cell line data is presented with AsPC-1 data at the top, followed next by BxPC-3, Capan-2, CFPAC-1, and finally MaPaCa-2 on the bottom. Referring to Figure 1D, the benefit of prolonged exposure to low concentrations of SN-38 was also observed when combined with 5-FU (20.7 mM for 48h) or oxaliplatin (12.3 mM for 4h). Both combinations also increased sensitivity of resistance cell lines to prolonged low-dose SN-38.

Figure 2 is two line graphs that depict cell viability following treatment with SN-38 as a single agent or the combination of SN-38 and oxaliplatin. BxPC-3 (Figure 2A) or CFPAC-1 (Figure 2B) cells were treated for 4h or 72h, washed and then incubated for an additional 24h or 144h with fresh media, following which cell viability was assessed. The data traces are labeled "1" (SN-38 alone for four hours followed by a 24 hour incubation; "2" SN-38 + oxaliplatin for four hours followed by a 24 hour incubation; "3" SN-38 alone for 72 hours followed by a 144 hour incubation; and "4" SN-38 + oxaliplatin for 72 hours followed by a 144 hour incubation. Treatment of the cells with a combination of SN-38 and oxaliplatin decreased the IC-50 when cells were treated for 4h only as compared to treatment with single agents in both cell lines tested.

Testing of cell line-derived and patient-derived xenograft models of pancreatic cancer in Example 2 demonstrated improved anti-tumor activity of liposomal irinotecan relative to exposure-matched doses of non-liposomal irinotecan. In the mouse animal studies in Example 2, a dose of "x" mg/kg liposomal irinotecan provides about the same exposure to the topoisomerase 1 inhibitor (irinotecan and/or SN-38) as a dose of "5x" non-liposomal irinotecan (CPT-11). The liposomal irinotecan consistently improved tumor growth inhibition and survival

relative to non-liposomal irinotecan in preclinical models, both as a monotherapy and in combination with 5-FU and oxaliplatin. The addition of MM-398 to 5-FU and/or oxaliplatin did not exacerbate the baseline toxicities of these agents, including weight loss and neutropenia, and tolerability could be further improved by delaying the administration of oxaliplatin to 1 day post-MM-398. These findings illustrate the therapeutic potential of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and support an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2).

An animal model of the FOLFIRINOX regimen was tested against the MM-398 + 5-FU/LV + oxaliplatin regimen in a pancreatic tumor xenograft mouse model. Liposomal irinotecan (MM-398) performed better than conventional (non-liposomal) irinotecan (CPT-11) at equivalent exposure doses (5 mg/kg MM-398 vs. 25 mg/kg free IRI) in the BxPC-3 pancreatic xenograft cancer models (Example 2) either alone (e.g., Figure 3A), or in combination with oxaliplatin and/or 5-FU (e.g., Figure 3B).

In the mouse model tested in Example 2, efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3) was evaluated. Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with free irinotecan (IRI), MM-398, 5-FU, oxaliplatin (Ox) or control was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. Figure 3A depicts a line graph representing tumor growth after treatment with various individual treatment agents. Figure 3B depicts a line graph representing tumor growth after treatment with various combinations of treatment agents.

Efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3). Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. In comparison to Figure 4A (discussed below), doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU demonstrate that

the MM-398-containing doublet and triplet regimens inhibit tumor growth significantly better than the IRI-containing regimens. The addition of oxaliplatin to the doublet combinations of FOLFIRI or MM-398+5-FU/LV causes a slight increase in tumor growth inhibition (Figure 3B: compare IRI + 5FU to IRI + 5FU +Ox for FOLFIRI vs. FOLFIRINOX; compare nal-IRI + 5FU to nal-IRI + 5FU + Ox for MM-398+5-FU/LV vs. MM-398+5-FU/LV+Ox). However, comparison of FOLFIRI versus the MM-398+5-FU/LV doublet (IRI + 5FU vs. nal-IRI + 5FU), and FOLFIRINOX vs. the MM-398+5-FU/LV+Ox triplet (IRI + 5FU +Ox vs. nal-IRI + 5FU + Ox), demonstrates significantly more tumor growth inhibition with the MM-398-containing regimens. Further, the MM-398-containing doublet regimen performed better than the FOLFIRINOX triplet (nal-IRI + 5FU vs. IRI + 5FU +Ox), owing to the improved efficacy of MM-398 compared to conventional irinotecan.

Single agent results of the individual treatments are shown in Figure 4A, demonstrating that MM-398 significantly inhibits tumor growth compared to free IRI. Figures 4A and 4B are two line graphs depicting tumor growth in mouse xenograft models following intravenous treatment with saline (control, circles), 5 mg/kg oxaliplatin (triangles), 5 mg/kg MM-398 (light squares), or the combination of BxPC-3 (Figure 4A) or CFPAC-1 (Figure 4B) tumor cells were implanted subcutaneously in mice. Treatment was initiated after tumors were well established, and treatments were given four times (BxPC-3 model) or three times (CFPAC-1 model) at the time points indicated by dashed lines on the graphs.

Figures 5A, 5B, 5C, 6A, 6B, 6C, 6D and 7 are graphs obtained by measuring tumor growth inhibition in mice following various treatments. Tumor cells (PDX model 19015) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone, or in combination with 5-FU or 5-FU + oxaliplatin, was initiated. Treatment doses are indicated in the figure beside each treatment, and were given 4 times.

Figures 5A-5C are three line graphs depicting tumor growth inhibition in mice following various treatments. Tumor cells, PDX 19015 model, were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan as monotherapy, or in combination with 5-FU and

Oxaliplatin, was initiated. Treatment doses are indicated in the legend beside each treatment, and were given four times, at time points indicated by dashed lines on the graphs. The addition of 5-FU to MM-398 or non-liposomal irinotecan significantly improved tumor growth inhibition relative to the respective monotherapies. The addition of oxaliplatin to MM-398 + 5-FU further improves response by significantly delaying tumor progression as compared to MM-398 monotherapy. The delay in tumor progression was not significant in the group treated with the double therapy of MM-398 + 5-FU. Figure 5A is a line graph comprising data from all of the combinations (both those with MM-398 and those with irinotecan), and shows that the combination of MM-398, oxaliplatin, and 5-FU resulted in the most inhibition of tumor growth (lowest line trace), although the combination of MM-398 and 5-FU also inhibited tumor growth (next lowest line). Figure 5B is a line graph comprising data from the MM-398 combinations only (no irinotecan combinations or control line) for the purpose of comparison. As can be seen in the graph, the triple combination treatment resulted in the most tumor growth inhibition (lowest line), and the double combination of irinotecan and 5-FU (middle line) was better than MM-398 alone (highest line) in inhibiting tumor growth. Figure 5C is a subset of the same data that allows comparison of the oxaliplatin combinations to the saline control.

Figure 6A is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (MM-398) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan). The data in Figure 6A shows a significantly greater reduction in the percent tumor volume change for administration of 10 mg/kg liposomal irinotecan (MM-398) compared to non-liposomal irinotecan (CPT-11) at 50 mg/kg, each administered on days 0, 7, 14 and 21 followed by observation for a total of about 60 days. Figure 6B is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (MM-398), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU. Mice receiving the combination of liposomal irinotecan (MM-398, also called MM-398) with 5FU and oxaliplatin on days 0, 7, 14 and 21 showed significantly reduced tumor volume percent change through the observation period of

about 60 days, compared to mice receiving the combination of non-liposomal irinotecan (CPT-11) with oxaliplatin and 5-FU on days 0, 7, 14 and 21. Referring to Figure 6C, the addition of oxaliplatin to MM-398 + 5-FU significantly improves progression free survival of mice bearing PDX 19015 tumors, as compared to the control group and MM-398 monotherapy. The difference between MM-398 + 5FU and MM-398 monotherapy is not statistically significant. Referring to Figure 6D, the addition of 5-FU and oxaliplatin to MM-398 significantly improve overall survival relative to the control group. No benefit of added 5-FU or oxaliplatin was observed with non-liposomal irinotecan. Referring to Figure 7, the addition of oxaliplatin to MM-398 + 5-FU significantly delays tumor progression relative to MM-398 monotherapy, as indicated by significantly reduced tumor volume at day 35.

Figure 8 is a table showing results of tumor growth and survival in mice following various treatments. Tumor cells (PDX 19015 model) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone (monotherapy), or in combination with 5-FU (NAPOLI, double therapy) or 5-FU + oxaliplatin (NAPOX, triple therapy), was initiated. Mice treated with the triple therapy, NAPOX (50%) had the best Overall Response Rate (ORR), as compared to double NAPOLI (38%), or monotherapy MM-398 monotherapy (0%). Further, triple therapy treated mice also had a better Disease Control Rate (DCR): NAPOX (75%), NAPOLI (63%), MM-398 monotherapy (38%), and Progression Free Survival (PFS): NAPOX was 47 days, relative to 36.5 days for NAPOLI and 12 days for MM-398 monotherapy. NAPOX PFS was significantly better than the monotherapy, whereas NAPOLI is not significantly better than the monotherapy. Notably, the combination of liposomal irinotecan with 5FU and oxaliplatin was better tolerated than the combination of an SN-38 exposure-matched dose of non-liposomal irinotecan with 5FU and oxaliplatin in a mouse tolerability study over 100 days. Figure 9 is a graph showing the body weight of mice after administration of various regimens: a saline control, liposomal irinotecan (MM-398), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin. Liposomal irinotecan improved tolerability in a mouse model following repeated dosing in mice relative to non-liposomal irinotecan when combined with 5-FU and oxaliplatin. Significance

was determined by ordinary 2-way analysis of variance (ANOVA). The regimens were administered on days 0, 7, 14 and 21 of the study. The administration of 10 mg/kg liposomal irinotecan and the 50 mg/kg dose of non-liposomal free irinotecan (CPT11) provide a comparable dose of SN-38 to tumor cells in the mouse model.

The tolerability of combinations of MM-398 liposomal irinotecan and oxaliplatin was improved in mouse models when the oxaliplatin was administered one day after the administration of the MM-398. Figures 10A and 10B depict line graphs demonstrating the toxicities associated with MM-398 and oxaliplatin given as monotherapy or combined therapy given concurrently (A) or staggered, with oxaliplatin given 1 day after MM-398 administration (B). Co-administration of MM-398 and oxaliplatin leads to significant toxicities as measured by loss of body weight, whereas delaying oxaliplatin administration by 24h after MM-398 does not lead to significant changes in body weight.

Figure 11A-11F are bar graphs depicting hematological and liver toxicities following treatment with MM-398 with or without oxaliplatin given either concurrently or sequentially with MM-398. Hematological toxicities (A-C) were improved by delayed administration of oxaliplatin. Liver enzymes (D-F) remained comparable to monotherapies when oxaliplatin administration was delayed.

These preclinical findings support the therapeutic use of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2). Figure 12 depicts a graphical representation of the study design employing the combination of MM-398 + 5-FU/LV + oxaliplatin in (Arm 1) and MM-398 + 5-FU/LV (Arm 2), and nab-paclitaxel + gemcitabine (Arm 3) as described herein.

For example, use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of: (a) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form

of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (b) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (c) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (d) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient, wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (e) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; (f) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; or (g) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2-85mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil, wherein the administration of the oxaliplatin begins 2 hours

after completing each administration of the liposomal irinotecan. Each of these exemplary uses can be modified to replace the doses of liposomal irinotecan, oxaliplatin, leucovorin and 5-flurouracil disclosed herein in the following passages relating to these specific components. Sometimes the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes. Sometimes, the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

As provided herein, irinotecan can be administered in an irinotecan liposome preparation. Preferably, the liposomal irinotecan is irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"), the formulation referred to herein as "MM-398" (also known as PEP02, see US 8,147,867) is a form of "nanoliposomal irinotecan" (also called "irinotecan liposome" or "liposomal Irinotecan"). MM-398 is irinotecan as the irinotecan sucrose octasulfate salt encapsulated in a nanoliposome drug delivery system.

The liposomal irinotecan can be a pharmaceutical composition prepared for human intravenous administration. For example, the liposomal irinotecan may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of liposomal irinotecan may be diluted, e.g., in 500 mL of 5% dextrose injection USP, to provide a variety of concentrations, for example, 5 mg/mL, and may be infused over a 90 minute period.

The active ingredient of the MM-398 injection, irinotecan, is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38. SN-38 is cleared via glucuronidation, (for which major pharmacogenetic differences have been shown),

and biliary excretion. These drug properties contribute to the marked differences in efficacy and toxicity observed in clinical studies with irinotecan.

The liposomal irinotecan can be a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space that contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for every 200 phospholipid molecules.

The amount of liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 180 mg/m^2, preferably 60 mg/m^2 when administered in combination with oxaliplatin and 5-fluorouracil for treatment of pancreatic cancer (dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt). The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received MM-398, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m^2 (amount of irinotecan base, equivalent to 60 -180 mg/m^2 dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt) and 353 patients with cancer using population pharmacokinetic analysis. Over the dose range of 50 to 155 mg/m^2, the C_{max} and AUC of total irinotecan increases with dose. Additionally, the C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

The combination treatment described herein encompasses administration of MM-398 liposomal irinotecan in combination with multiple additional active agents: oxaliplatin, leucovorin and 5-fluorouracil, in doses and schedules to human patients with metastatic pancreatic cancer not previously treated with a prior chemotherapeutic agent in the metastatic setting as described herein.

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also

interferes with RNA synthesis. An exemplary effective amount of 5-fluorouracil administered to a human patient can range from about 2,000 mg/m^2 to about 3,000 mg/m^2. In some embodiments, the amount of 5-fluorouracil administered to the human patient is 2,400 mg/m^2.

Leucovorin is optionally administered prior to the 5-fluorouracil. Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase. Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levo-leucovorin") has also been approved by the FDA for treatment of cancer. The dosage of leucovorin is that of the racemic mixture containing both dextro (d) and levo (l) isomers, or optionally the (l) form of leucovorin at half the dosage of the (l + d) racemic form. An exemplary effective amount of leucovorin administered to the human patient can include an amount of (l)-form leucovorin ranging from about 100 mg/m^2 to about 300 mg/m^2. In some embodiments, the amount of (l)-form leucovorin administered to the human patient is 200 mg/m^2. In other embodiments, the leucovorin administered is the (l + d)-form of leucovorin, in an amount ranging from about 200 mg/m^2 to about 600 mg/m^2. In some embodiments, the amount of (l + d)-form of leucovorin administered is 400 mg/m^2.

Oxaliplatin is a platinum-based drug that acts as a DNA cross-linking agent to effectively inhibit DNA replication and transcription, resulting in cytotoxicity which is cell-cycle non-specific. Oxaliplatin is typically used in combination with infusional 5-FU/LV, and is approved for use in advanced colorectal cancer (refer to package insert for more details). The effective amount of oxaliplatin administered to the human patient can range from about 30 mg/m^2 to about 150 mg/m^2, for example, from about 40 mg/m^2 to about 100 mg/m^2, or an amount of oxaliplatin of

50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, or 95 mg/m^2.

Dose modifications may be made to methods of administering the combination treatment described herein as a result of adverse events, include hematological and non-hematological adverse events.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of MM-398 administered according to the embodiments herein. In some embodiments, the dose of MM-398 is modified according to Table 1.

Table 1A: Examples of Dose Modifications for MM-398 (salt)

Toxicity **NCI CTCAE v4.0**	**Occurrence**	**MM-398 adjustment in patients receiving** **60 mg/m^{2‡} (salt)**	**Patients homozygous for UGT1A1*28 without previous increase to** **60 mg/m^2 (salt)**
Grade 3 or 4 adverse reactions	Withhold MM-398. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1 or baseline grade resume MM-398 at:		
	First	45 mg/m^2	35 mg/m^2
	Second	35 mg/m^2	30 mg/m^2
	Third	Discontinue MM-398	Discontinue MM-398
Interstitial Lung Disease	First	Discontinue MM-398	Discontinue MM-398
Anaphylactic Reaction	First	Discontinue MM-398	Discontinue MM-398

In some embodiments, the first, second or any subsequent dose of MM-398 can be reduced by 20-30% (including dose reductions of 20%, 25% and/or 30%) in response to patient tolerability considerations such as an adverse reaction to a first or subsequent dose of MM-398 and/or other antineoplastic agent, and/or identifying a patient as being homozygous for the

UGT1A1*28 allele. In some embodiments, the second or subsequent dose of MM-398 is reduced by about 20%, 25% or 30% (e.g., a dose reduction from 60 mg/m2 to . In some embodiments, the dose of MM-398 is reduced by 25%. In some embodiments, the dose of MM-398 is reduced by 30%. In some embodiments, the reduced dose of MM-398 is in a range starting from 30 mg/m^2 to (and including) 55 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 60 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 45 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 35 mg/m^2.

Other dose reduction schedules are provided Tables 1B-1E below. When the starting (initial) dose of MM-398 is 60 mg/m^2, 5FU 2400mg/m^2, LV(l+d) 400mg/m^2 and Oxaliplatin is either 85mg/m2 OR 60mg/m2, then the first dose reduction in response to a grade III or IV hematotoxicity is preferably a 25% dose reduction for each of the MM-398, 5-FU and Oxaliplatin doses for each administration of the antineoplastic therapy. For persistent toxicities despite the first dose reduction, an additional 25% dose reduction in each of the antineoplastic agents of MM-398, 5-fluorouracil and oxaliplatin is preferred. Further toxicity will then lead to discontinuation of treatment in some instances. For non-hematologic toxicities, the same dose reduction schema can be followed as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which can be selected based on the medically appropriate dose for the patient.

Table 1B Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	1800
Second Reduction	35	35	1350

Table 1C Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	1800
Second Reduction	35	45	1350

Table 1D Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	2400
Second Reduction	35	35	1800

Table 1E Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	2400
Second Reduction	35	45	1800

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of Oxaliplatin administered according to the embodiments herein. In some embodiments, the dose of Oxaliplatin is reduced by 20-30%. In some embodiments, the, the dose of Oxaliplatin is reduced by 20%. In some embodiments, the, the dose of Oxaliplatin is reduced by 25%. In some embodiments, the, the dose of Oxaliplatin is reduced by 30%. In some embodiments, the reduced dose of Oxaliplatin is in a range from 30 mg/m^2 to 75 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 75 mg/m^2. In some embodiments,

the dose of Oxaliplatin is reduced to 65 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 60 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 34 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of 5-fluorouracil administered according to the embodiments herein. In some embodiments, the dose of 5-fluorouracil is reduced by 20-30%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 20%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 25%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 30%. In some embodiments, the reduced dose of 5-fluorouracil is in a range from 1000 mg/m^2 to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1350 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1200 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include further reducing or otherwise modifying the dose of MM-398, Oxaliplatin and/or 5-fluorouracil administered according to the embodiments herein.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of more than one of MM-398, Oxaliplatin and 5-fluorouracil administered according to the embodiments herein.

Additional dose modifications for MM-398, Oxaliplatin and/or 5-fluorouracil can be found in the respective Package Inserts, which are incorporated herein by reference.

In one embodiment, the method of administering the combination treatment comprises 34, 45, or 60 mg/m^2 of liposomal irinotecan, 34, 42, 45, 60 or 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 1,200, 1,350,

1,800 or 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Thus, in some embodiments, the method of administering the combination treatment to treat the metastatic adenocarcinoma of the pancreas in the human patient comprises:

(A) (i) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-

FU; (xvii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (B) (i) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 45 mg/m^2 of liposomal irinotecan, 60

mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; or (C) (i) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400

mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or(xx) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU.

Liposomal irinotecan is preferably administered intravenously, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin. In one embodiment, liposomal irinotecan is administered prior to oxaliplatin, 5-FU and leucovorin. In another embodiment, leucovorin is administered prior to 5-FU. In another embodiment, the MM-398 liposomal irinotecan is administered followed by administration of the oxaliplatin, followed by administration of the leucovorin, and followed by the administration of the 5-fluorouracil. In certain embodiments, the liposomal irinotecan is administered to the patient intravenously over 90 minutes. In another embodiment, the oxaliplatin is administered to the patient intravenously over 120 minutes. In another embodiment, 5-FU is administered intravenously over 46 hours. In one embodiment, the oxaliplatin is administered from about 6 to about 72 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered for example, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, or 72 hours, after administration of the liposomal irinotecan. In another embodiment, leucovorin is administered intravenously over 30 minutes. In various embodiments the liposomal irinotecan is MM-398. In various embodiments, the human patient with metastatic pancreatic cancer is pre-medicated with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan, and other active agents.

Further embodiments of the invention

The following methods and embodiments can be considered alone, in combination other embodiments in this section, or in combination with the methods disclosed above. The invention provides methods for treating pancreatic cancer in a human patient, such as in a patient not previously treated with a chemotherapeutic agent in the metastatic setting, the method comprising administering to the patient liposomal irinotecan, also referred to as MM-398 (e.g., irinotecan sucrose octasulfate salt liposome injection) in combination with oxaliplatin, leucovorin and 5-FU.

1. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

2. The method of embodiment 1, wherein the amount of MM-398 liposomal irinotecan administered is administered is 60 mg/m^2 or 80 mg/m^2.

3. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to the subject 60 mg/m^2 of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

4. The method of any one of embodiments 1-3, wherein the amount of oxaliplatin administered is from about 50 mg/m^2 to about 100 mg/m^2, such as about 60 mg/m^2 to about 85 mg/m^2, for example 60 mg/m^2, 75 mg/m^2, or 85 mg/m^2.

5. The method of any one of embodiments 1-4, wherein the leucovorin administered at a dosage of 400 mg/m^2 of the (l + d) racemic form, or 200 mg/m^2 of the (l) form.

6. The method of any one of embodiments 1-5, wherein the amount of 5-FU administered is 2,400 mg/m^2.

7. The method of any one of embodiments 1-6, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU are administered at least once, such as wherein the MM-398, oxaliplatin, leucovorin, and 5-FU are administered on days 1 and 15 of a 28-day cycle.

8. The method of any one of embodiments 1-7, wherein multiple cycles are administered.

9. The method of any one of embodiments 1-8, wherein the pancreatic cancer is adenocarcinoma of the pancreas, such as unresectable, locally advanced or metastatic adenocarcinoma of the pancreas, for example, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas; or wherein the metastatic pancreatic cancer is an exocrine metastatic pancreatic cancer selected from the group consisting of Duct cell carcinoma, Acinar cell carcinoma, Adenosquamous carcinoma, Cyst adenocarcinoma (serous and mucinous types), Giant cell carcinoma, Invasive adenocarcinoma associated with cystic mucinous neoplasm or intraductal papillary mucinous neoplasm, Mixed type (ductal-endocrine or acinar-endocrine), Mucinous carcinoma, Pancreatoblastoma, Papillary-cystic neoplasm (Frantz tumor), Papillary mucinous carcinoma, Signet ring carcinoma, Small cell carcinoma, Unclassified, Undifferentiated carcinoma, serous cystadenocarcinoma, and Solid and Pseudopapillary tumors.

11. The method of any one of embodiments 1-10, wherein the oxaliplatin is administered to the patient prior to the leucovorin, such as wherein the leucovorin is administered to the patient prior to the 5-FU, optionally wherein the MM-398 liposomal irinotecan is administered to the patient prior to the oxaliplatin, leucovorin, and 5-FU.

12. The method of embodiment 11, wherein the MM-398 is administered over 90 minutes, followed by administration of the oxaliplatin over 120 minutes, followed by administration of the leucovorin over 30 minutes, followed by the administration of the 5-FU over 46 hours.

In a particular embodiment, a human patient with metastatic adenocarcinoma of the pancreas who has not previously been treated with any chemotherapeutic agent in the metastatic setting, is treated with a combination regimen of the present disclosure, the method comprising, intravenously administering to the patient, beginning on day 1 of a 2-week cycle, 80 mg/m^2 of MM-398 liposomal irinotecan over 90 minutes, followed by 60-85 mg/m^2 oxaliplatin, followed by 200 mg/m^2 of the (*l*) form of leucovorin, or 400 mg/m^2 of the (*l+d*) racemic form of leucovorin, followed by 2,400 mg/m^2 5-FU, wherein the human patient is treated with one or multiple cycles. In the embodiments disclosed herein, the effective amount of MM-398 liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 80 mg/m^2. In various embodiments, the amount of MM-398 liposomal irinotecan administered to the human patient is 60 mg/m^2 or 80

mg/m^2. In the embodiments disclosed herein, the effective amount of Oxalyplatin administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 85 mg/m^2. In various embodiments, the amount Oxalyplatin administered to the human patient is 60 mg/m^2 or 85 mg/m^2. In one variant of this embodiment, oxaliplatin is administered over 120 minutes, leucovorin is administered over 30 minutes, and 5-FU is administered over 46 hours.

Examples

Example 1: *In vitro* pancreatic cancer cell exposure to topoisomerase 1 inhibitor

Simulated tumor exposure of SN-38 in patients administered with free irinotecan or MM-398 were shown in Figure 1A. MM-398 is shown to result in prolonged SN-38 duration in tumors compared to free irinotecan (CPT-11). The effect of various SN-38 durations on cell growth inhibition was studied in a panel of pancreatic cell lines (AsPC-1, BxPC-3, Capan-2, CFPAC-1, and MiaPaCa-2). Figure 1B illustrates the in vitro conditions for mimicking this clinically comparable SN-38 exposure of the 2 drugs, where cells exposed to SN-38 at high concentrations for a short period of time approximates for free irinotecan, and at low concentrations for a long period of time for MM-398. The results and experimental conditions are summarized in Figure 1C. For example, cells incubated with 139 nM of SN-38 for 144h vs. 417 nM for 24h have similar SN-38 tumor exposure ratios of MM-398 vs. free irinotecan in patient tumors. Under these clinically relevant conditions, prolonged exposure (i.e. MM-398) primarily resulted in more pancreatic cancer cell growth inhibition compared to short exposure at high concentrations (i.e. free irinotecan). Similar results were also obtained when SN-38 were combined with 5-FU or oxaliplatin, demonstrating that prolonged exposure also led to increased cell growth inhibition when combined with these other chemotherapeutics agents that are used in the FOLFIRINOX regimen.

Example 2: Evaluation of *in vivo* tolerability and efficacy of combination therapies in an animal model

<u>BxPC-3 and CFPAC-1 mouse xenograft studies</u> (efficacy):

Tissue culture: BxPC-3 cells were cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin. CFPAC-1 cells were also cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin.

Animals: Experiments were performed according to approved guidelines. Female NOD.scid mice were obtained from Charles River Laboratories (Wilmington, MA). BxPC-3 or CFPAC-1 cells were inoculated into the right hind flank at 5e6 cells in a total volume of 50 uL per mouse. Eight animals were treated per group, unless otherwise indicated. Animals were randomized and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 2 weeks post post-final dose.

PDX19015 mouse xenograft study (efficacy and tolerability):

Animals: Experiments were performed according to approved guidelines. Female CB.17 SCID mice were obtained from Roswell Park Cancer Institute (Buffalo, NY), initially at 6-8 weeks of age. Per treatment group, 8 animals were treated, unless otherwise indicated. Tumor pieces were derived from donor mice and engrafted subcutaneously. Animals were randomized and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured twice weekly during the dosing cycle, then once weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 100 days post-first dose. Tolerability: Mouse weights were measured once weekly to

monitor treatment tolerability. Mice were euthanized when body weight declined to ≥20% below baseline, or they exhibited overt signs of poor general health.

Delayed dosing of oxaliplatin:

Animals: Experiments were performed according to approved guidelines. Female CD-1 mice were obtained from Charles River Laboratories (Wilmington, MA). Tolerability studies were performed in naïve (non-tumor-bearing) mice. Three animals were treated per group.

Treatment tolerability: Agents were administered intravenously at their pre-defined maximum tolerated doses (MM-398, 50mg/kg; oxaliplatin, 17mg/kg). Each drug was administered individually, or in combination. Combinations were given in one of 3 independent dosing schedules: coinjection (drugs administered simultaneously), MM-398 given on day 1 and oxaliplatin given on day 2 (24h delay), or MM-398 given on day 1 and oxaliplatin given on day 4 (72h delay). A single administration of each drug was given. Mouse body weights were measured daily for up to 2 weeks post-treatment. Mice were euthanized when body weight declined to ≥20% below baseline, they exhibited overt signs of poor general health, or at 2 weeks post-treatment (end of study).

Measurement of hematologic and liver toxicities: At the end of study, terminal bleeds were performed for each mouse via cardiac puncture. Hematologic function (blood cell count) was measured by Hemavet (Drew Scientific, Miami Lakes, FL), according to manufacturer's protocol. Liver function (enzyme levels) was measured by CatalystDx (Idexx Laboratories, Westbrook, ME) according to the manufacturer's protocol.

Example 3: Treatment of Pancreatic Cancer

As schematically shown in Figure 12, the present study is an open-label, phase 2 comparative study to assess the safety, tolerability, and efficacy of MM-398 in combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with metastatic pancreatic adenocarcinoma who have not received prior chemotherapy. This study assesses the following regimens: (1) MM-398 + 5-FU/LV + oxaliplatin (Arm 1), (2) MM-398 + 5-FU/LV (Arm 2) and (3) nab-paclitaxel + gemcitabine (Arm 3).

This phase 2 study evaluates the preliminary safety and efficacy of MM-398 + 5-FU/LV with or without oxaliplatin versus nab-paclitaxel + gemcitabine in patients with previously untreated mPAC. The study may also provide important information on the impact of MM-398 combination treatment on patient HRQL and identify potential biomarkers of response.

In the study, MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen. The addition of oxaliplatin to the NAPOLI-1 regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398 prolonged PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the efficacy of FOLFIRINOX.

A modified triplet combination regimen of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU)/leucovorin is provided herein, whereby no bolus of 5-FU will be administered. The target dose of oxaliplatin (60-85 mg/m^2) is evaluated in the Arm 1 combination regimen with the continuous infusion dose of 5-FU (excluding the bolus), and the every 2 week dose of MM-398 previously shown to be tolerable and efficacious in combination with 5-FU. Note that with MM-398 dosing, the C_{max} of SN-38 is expected to be lower than would be expected for standard dosing with free irinotecan.

The study is conducted in two parts, as illustrated in the schematic of Figure 12: 1) a safety run-in of the MM-398 + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the MM-398 + 5-FU/LV + oxaliplatin regimen, the MM-398 + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), and a nab-paclitaxel + gemcitabine control arm.

Part 1:

Part 1 consists of an open-label safety run-in of the combination regimen in Arm 1: MM-398 + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and MM-398 + 5-FU/LV has been demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore was not included in this part of the study. The safety run-in enrolls small cohorts of patients following a traditional 3 + 3 dose

escalation design in order to confirm the target dose of oxaliplatin. Dose limiting toxicities (DLTs) are evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2nd dose of study treatment if there is a treatment delay in cohorts of patients to determine if the target combination dose is tolerable (note: the target combination dose is based on the established dose of the FOLFIRINOX regimen)). If there are no DLTs within the safety evaluation period, then the subsequent cohort is initiated following agreement between the Investigators, Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort is expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose is considered to exceed the safety and tolerability criteria of the combination, and the dose is not be escalated further; however, lower doses can be explored. The Part 2 dose is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Additionally, UGT1A1*28 allele status is considered when evaluating DLTs. Based on previous experience with irinotecan, individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan, in a study of 66 patients who received single-agent irinotecan (350 mg/m^2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. Importantly, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of accompanying life threatening neutropenia is described (for details refer to the prescribing information for irinotecan). Population PK studies of MM-398 have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study, no differences in toxicity were seen in cohorts of heterozygous or WT patients, and DLTs of diarrhea with or without accompanying dehydration or fatigue, were seen in both cohorts. For these reasons, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results are not required prior to the first dose of MM-398 on this study and the starting

dose for all patients will be 80 mg/m^2. However, if patients are known to be homozygous for UGT1A1*28, the dose of MM-398 may be reduced as described herein.

Part 2:

Part 2 consists of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either MM-398 + 5-FU/LV + oxaliplatin, MM-398 + 5-FU/LV, or nab-paclitaxel + gemcitabine. The randomization is stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1).

The following adverse events are common (≥ 40%) with past oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the MM-398-containing combination regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. Additional adverse events may be anticipated, as described in the package insert for oxaliplatin, including allergic and anaphylactic reactions. In a Phase 3 study of the FOLFIRINOX combination, the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia. Considering these expected toxicities, Arm 1 is evaluated for safety and tolerability in Part 1 of the study as described below.

A dose of oxaliplatin of 85 mg/m^2 is the target dose for Part 2 of this study. The purpose of Part 1 is to confirm whether this dose is compatible when MM-398 is used instead of conventional irinotecan. In case there are any unexpected toxicities, 3 to 6 patients are initially treated at a lower dose of oxaliplatin (60 mg/m^2, see Table 1) prior to administration of oxaliplatin at the highest proposed dose of 85 mg/m^2. The dose of the triplet combination to be administered in Part 2 of the study is defined as the highest dose level at which a DLT is experienced by fewer than 2 patients in a cohort of 3 to 6 patients. If one patient experiences a treatment-related toxicity that qualifies as a DLT, up to 3 additional patients are enrolled at that dose level, for no more than 6 total patients per cohort. If no additional DLTs are observed, the dose escalation resumes. If a second patient experiences a treatment-related toxicity that qualifies as a DLT at

that dose, that dose is considered to exceed the optimal safety and tolerability criteria of the combination. The dose to be used in Part 2 is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Dosing of patient cohorts begins at dose level -1 with planned escalation to dose level -2B (target dose), in which the dose for one of the three drugs is increased while the other two drugs will maintain a constant dose. If the -1 dose level is evaluated and deemed to be safe, escalation to the -2B dose level may be initiated. Any decisions to de-escalate, as well as enrollment at alternative doses following de-escalation, must be made according to the established decision process for dose escalation, as described herein. Planned dose escalation for the Arm 1 combination regimen is outlined in Table 2 below; additional details on dose administration as described herein in the section "Study Treatment".

Table 2 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Arm 1: MM-398 + 5-FU/LV + Oxaliplatin

The order of the infusions to be administered in the clinic is as follows: MM-398 administered first, followed by oxaliplatin, then LV, followed by 5-FU.

In Part 1, patients receive the oxaliplatin infusion 2 hours after the completion of the MM-398 infusion. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly after completion of the MM-398 infusion. If any grade 3 or higher infusion reactions are seen in Part

2 patients, the DSMB may elect to revert back to administration of oxaliplatin two hours after the completion of the MM-398 infusion.

Arm 1 Premedication

All patients must be premedicated prior to MM-398 infusion, 5-FU/LV infusion, and oxaliplatin infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan, 5-FU, and oxaliplatin administration, or the Summary of Product Characteristics (SmPC) for sites located in the European Union (EU). Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

Arm 2: MM-398 + 5-FU/LV

The order of the infusions to be administered in the clinic will be as follows: MM-398 will be administered first, followed by LV, followed by 5-FU.

Arm 2 Premedication

All patients must be premedicated prior to MM-398 infusion and 5-FU/LV infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan and 5-FU administration, or the SmPC for sites located in the EU. Atropine may be prescribed prophylactically, according to standard institutional practices, for patients who experienced acute cholinergic symptoms in the previous cycles.

Doses and Administration of MM-398 (Arms 1 and 2)

MM-398 is administered by intravenous (IV) infusion over 90 minutes (±10 minutes) every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) or normal saline to a final volume of 500 mL. Care should be taken not

to use in-line filters or any diluents other than D5W or normal saline. MM-398 can be administered at a rate of up to 1 mL/sec (30 mg/sec).

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

Doses and Administration of 5-FU and Leucovorin (Arms 1 and 2)

Leucovorin is administered at a dose of 400 mg/m^2 of the (l + d)- racemic form, or (l) form 200 mg/m^2, as an IV infusion over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle

5-FU is administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle

Leucovorin should be reconstituted per the instructions on the package insert, SmPC or standard institutional guidelines for reconstitution of leucovorin.

Leucovorin should be administered prior to the 5-FU infusion (on Arm 1, leucovorin will be given concurrently with oxaliplatin). Actual dose of 5-FU and leucovorin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

Doses and Administration of Oxaliplatin (Arm 1 only)

In Part 1, oxaliplatin is administered at increasing dose levels as indicated in Table 2 (from 60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle

In Part 2, oxaliplatin is administered at a dose of 85 mg/m^2, IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle (if target dose is confirmed in accordance with methods described herein).

Oxaliplatin should be prepared according to the instructions on the package insert, SmPC or per standard institutional guidelines for preparation and administration of oxaliplatin.

Oxaliplatin should be administered following MM-398 infusion; in Part 1, the first 3 patients in Dose Level 1 begin the oxaliplatin infusion two hours after the completion of the MM-398 infusion. Actual dose of oxaliplatin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose is allowed for ease of dose administration.

Arm 3: nab-Paclitaxel + Gemcitabine

The order of the infusions to be administered in the clinic is as follows: nab-paclitaxel will be administered first, followed by gemcitabine.

Arm 3 Premedication

All patients receiving nab-paclitaxel and gemcitabine should be pre-medicated per the respective package inserts. If different institutional guidelines exist for premedication of weekly nab-paclitaxel and/or gemcitabine, the investigator should use their standard practice or the SmPC for sites located in the EU.

Doses and Administration of nab-Paclitaxel and Gemcitabine (Arm 3)

The nab-paclitaxel will be administered at 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

The gemcitabine will be administered at 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

Dose Limiting Toxicities (DLTs)

For MM-398 administered in combination with 5-FU/LV and oxaliplatin, the following adverse events are considered as dose limiting toxicities (DLTs) if they occur during the first cycle of treatment and are deemed related to the study treatment regimen:

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia);
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection;
- Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity; and
- Any grade 4 non-hematologic toxicity with the specific exclusion of: Fatigue/asthenia < 2 weeks in duration, increases in alkaline phosphatase level, nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen), and diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

Any toxicity that is related to disease progression will not be considered a DLT.

The safety assessment period for purposes of DLT evaluation and dose escalation decisions is one cycle of treatment (i.e. 28 days; or 14 days after the 2nd dose of study treatment if there is a treatment delay according as described herein). The dose can escalate to the next level only after the safety data have been evaluated at the current dose level (once the last patient enrolled in the cohort completes the first cycle of treatment) and the criteria for safety and tolerability of the optimal dose have not been exceeded (see Section Part 2 dose definition). In addition, any drug-related toxicities of Grade 3 or higher that arise after Cycle 1 (if applicable) are assessed for their potential relationship to cumulative MM-398 or combination therapy doses and considered in the decision to escalate the dose. PK data may be available, but is not be required for decisions on dose escalation.

Inclusion Criteria	Exclusion Criteria
In order for inclusion into the study, patients must have/be: • Pathologically confirmed	Patients must meet all the inclusion criteria and none of the following exclusion criteria: • Prior treatment of pancreatic cancer in the

Inclusion Criteria	Exclusion Criteria
adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting ○ Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment ○ Part 2: must have metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed • Measurable or non-measurable disease as defined by RECIST v1.1 • ECOG performance status of 0 or 1 • Adequate biological parameters as evidenced by the following blood counts: ○ ANC > 1,500 cells/µl without the use of hematopoietic growth factors, ○ Platelet count > 100,000 cells/µl, and ○ Hemoglobin > 9 g/dL • Adequate hepatic function as evidenced by: ○ Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and ○ AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) • Adequate renal function as	metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) • Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) • Known metastasis to the central nervous system • Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction • History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. • Known hypersensitivity to any of the components of MM-398, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin • Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only) • Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: ○ Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion ○ NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure ○ Known historical or active infection with HIV, hepatitis B, or hepatitis C • Active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the

Inclusion Criteria	Exclusion Criteria
evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.72 m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean body weight should be used instead. • Normal ECG or ECG without any clinically significant findings • Recovered from the effects of any prior surgery or radiotherapy • ≥ 18 years of age • Agreeable to submit unstained archived tumor tissue for analysis, if available • Able to understand and sign an informed consent (or have a legal representative who is able to do so)	patient's participation in the trial or affect the study outcome • Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan • Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin • Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only) • Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results • Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 3 months following the last dose of study drug.

Dose Modifications

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03). All dose reductions for all arms should be based on the worst preceding toxicity.

Dosing may be held for up to 2 weeks from when it was due to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than 2 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor regarding risks and benefits of continuation. If oxaliplatin is not well tolerated in patients enrolled in Arm 1, oxaliplatin may be discontinued and patients may continue to receive MM-398 + 5-FU/LV at the discretion of the Investigator.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Dose Modifications

Prior to each dosing, patients must have: ANC ≥ 1500/mm^3, WBC ≥ 3500/ mm^3, Platelet count ≥ 100,000/mm^3 and Diarrhea ≤ Grade 1.

Treatment should be delayed to allow sufficient time for recovery to levels noted above, and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to ≥ 1500/mm^3 and the patient must have recovered from infection. For Grade 3 or 4 non-hematological toxicities, treatment should be delayed until they resolve to Grade 1 or baseline. Guidelines for dose adjustments of each individual treatment within the regimen are found in the tables below for Arm 1 (Table 3), and for Arm 2 (Tables 6 through 14). In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management should be followed.

For all tables below, patient should be withdrawn from study treatment if more than 2 dose reductions are required or if MM-398 reductions lower than 35 mg/m^2 are required. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well.

Treatment discontinuation that is required due to MM-398 or 5-FU toxicity will result in discontinuation from the study. However, for Arm 1, toxicity that requires discontinuation from oxaliplatin only (e.g. neuropathy) will result in the option to continue on study treatment with MM-398 + 5-FU/LV only for all future dosing.

Arm 1 Dose Modifications

The starting dose of ONIVYDE will be 60mg/m^2, 5FU 2400mg/m^2, LV 400mg/m^2 and Oxaliplatin either 85mg/m^2 or 60mg/ m^2. Dose reduction will be 25% reduction in all agents for any grade III-IV Hematotoxicity. For persistent toxicities despite the first dose reduction, and additional 25% dose reduction in all agents will occur. Further toxicity will then lead to discontinuation from trial.

For non-hematologic toxicities, the dose reduction will be the same dose reduction schema as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which will be as shown in Table 3.

Table 3: Arm 1 Dose Modifications

Worst Toxicity by CTCAE Grade	**MM-398**	**5-FU**	**Oxaliplatin**
Hematological Toxicities			
Grade 2 neutropenia (ANC <1500 - 1000 cells/ mm^3)	100 % of previous dose	100 % of previous dose	1st occurrence: 100% of previous dose

Grade 3 or 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia[a]	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	1st occurrence: Reduce dose from 85 mg/m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
≥ Grade 2 thrombocytopenia (Grade 2: platelets ≤ 75,000/mm^3 – 50,000/mm^3 OR Grade 3-4: platelets < 50,000/mm^3)	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	1st occurrence: Reduce dose from 85 mg/m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2

Other hematologic toxicities not specifically listed above	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[b]			
Grade 1 or 2, including diarrhea[c]	100 % of previous dose	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100 % of previous dose

Grade 3 or 4, including diarrhea[d] (except nausea and vomiting)	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% *except for Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Optimize anti-emetic therapy AND reduce dose by 25% ; if the patient is already receiving a reduced dose, reduce dose an additional 25%	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Grade 2 hand foot syndrome	100 % of previous dose[d]	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	100 % of previous dose
Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Discontinue therapy	No dose modifications required
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	No dose modifications required[e]	Discontinue therapy	No dose modifications required

Sensory neuropathy	No dose modifications required[e]	No dose modifications required[e]	Grade 2, persistent: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, recovers prior to next cycle: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, persistent: Discontinue therapy Grade 4: Discontinue therapy

[a]Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia.

[b]Asthenia and Grade 3 Anorexia do not require dose modification

[c]Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment

[d] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment

Arm 2 Dose Modifications

Dosing may be held for up to 3 weeks from when it was due, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Table 4

Grade 1: Transient flushing or rash, drug fever <38º C (<100.4º F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Table 5

Grade 1 • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2 • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition

• For all subsequent infusions, premedicate with diphenhydramine hydrochloride 25-50 mg IV
Grade 3 • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary • No further treatment with MM-398 will be permitted
Grade 4 • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table 6: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm^3 (Worst CTCAE grade)	MM-398 Dose for Next Cycle		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
≥ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose
< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 7: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below. Infusion reactions should be handled as described above.

Table 8: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
Grade 1 or 2 (2-3 stools/day > pretreatment or 4-6 stools/day > pretreatment)	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 9: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2

5-FU and Leucovorin Dose Modifications

Guidelines for 5-FU dose modifications are provided below. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for MM-398 infusion reaction management should be used.

5-FU Dose Modifications for Hematological Toxicities

Prior to the next dose in a cycle or prior to initiating a new cycle of therapy, the patients must have:

- ANC ≥ 1500/mm^3
- WBC ≥ 3500/mm^3
- Platelet count ≥ 75,000/mm^3 (according to the European summary of product characteristics for 5-FU, the platelets should have recovered to ≥ 100,000/mm^3 prior to initiating therapy)

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines provided in the table below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 10: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC (cells/mm^3)		Platelets (cells/mm^3)	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study

5-FU Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until all Grade 3 or 4 non-hematological toxicities resolve to Grade 1 or baseline. Guidelines for dose adjustment of 5-FU related toxicities are provided below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 11: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[c]

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25%[b]	Reduce dose by 25%[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25%[b], except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25%[b],except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study
[c] Asthenia and Grade 3 Anorexia do not require dose modification

*MM-398 Dose Modifications for UGT1A1*28 Positive Patients (Arms 1 and 2)*

Patients are tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of MM-398. All patients will begin dosing at 80 mg/m^2 (salt), however future doses may be reduced for patients who are positive (i.e. homozygous) for UGT1A1*28 7/7 genotype. For Part 1 patients receiving 80 mg/m^2 (salt) of MM-398: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m^2 (salt) after discussion between the PI, Sponsor and Medical Monitor. Any Part 1 patients who receive a reduced dose during Cycle 1 due to UGT1A1*28 homozygosity will not be evaluable for the cohort and are replaced.

Arm 3 Dose Modifications

Dose level reductions required due to toxicities related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 12.

Table 12: Dose Level Reductions for nab-Paclitaxel and Gemcitabine

Dose Level	**Nab-paclitaxel (mg/m^2)**	**Gemcitabine (mg/m^2)**
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reductions required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 13 and adjustments related to other toxicities are provided in Table 14.

Table 13: nab-Paclitaxel and Gemcitabine Dose Modifications at the Start of Each Cycle or Within a Cycle for Neutropenia and/or Thrombocytopenia.

Cycle Day	**ANC (cells/mm^3)**		**Platelet count (cells/mm^3)**	**Nab-paclitaxel / Gemcitabine**
Day 1	<1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were withheld:				

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Nab-paclitaxel / Gemcitabine
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = absolute neutrophil count

Table 14: nab-Paclitaxel and Gemcitabine Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves ≤ Grade 1; resume at next dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next dose level	

Disease Evaluation

Tumor responses are evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, to establish disease progression by CT or MRI. In addition, other imaging procedures, as deemed appropriate by the Investigator, are performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Investigators should select target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

Tumor assessments should be completed until it has been determined that the patient has progressive disease (in accordance with RECIST v1.1). For patients who do not have documented disease progression per RECIST v. 1.1 at the time of treatment termination, imaging studies should be continually performed into the follow-up period every 8 weeks until disease progression is documented. Continued imaging follow-up on schedule is recommended to reduce potential bias in the evaluations of the impacts of the experimental treatments on disease.

EORTC-QLQ-C30 and EQ-5D-5L (Part 2 Only)

Health-related quality of life (HRQL) is assessed by the EORTC-QLQ-C30 and EQ-5D-5L instruments. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. EQ-5D is a generic, preference-based measurement of HRQL. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to do.

Patients are required to complete both questionnaires at time points outlined in the Schedule of Assessments. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients for whom validated translations of the questionnaires are available will be required to complete the questionnaire.

Efficacy Analysis

In the assessments of efficacy, each MM-398-containing arm is compared to the control arm. Efficacy comparisons use stratified analyses, incorporating randomization strata. Each comparison uses 0.10 level one-sided testing to evaluate whether the MM-398 -containing arm improves the efficacy parameter. Confidence intervals are presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals are not adjusted for multiple comparisons. The primary efficacy comparisons are based on the ITT population, which includes all randomized patients.

Tumor evaluation is measured according to RECIST v1.1. For each patient, progression free survival time is determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical Progression of Disease (PD), per investigator using RECIST 1.1, or death from any cause,

whichever comes first. If the progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time is censored at the time of the last non-PD tumor assessment.

A primary analysis is conducted when the Week 24 progression-free status for all randomized patients can be determined, anticipated at approximately 24 weeks after the last patient is randomized. A subsequent analysis for PFS and other endpoints is performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients.

Primary Efficacy Analysis

In the intention-to-treat (ITT) analysis, a patient is considered to have achieved progression-free survival at 24 weeks if the patient has data to indicate the patient has not progressed at 24 weeks. That is, a patient is considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.

Patients who do not meet the 24-week progression-free achievement criteria (e.g. patients progressed/died up to Week 24, patients censored prior to Week 24), if progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment.

For each arm, the progression-free survival achievement rate at 24 weeks is estimated by the number of patients meeting the 24 week achievement criteria divided by the number of ITT patients in the arm. The rate estimates are presented with corresponding 95% confidence intervals. Each MM-398 containing arm is assessed for increase in rate relative to the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at 0.10 level of significance.

Secondary Efficacy Analyses

Progression-Free Survival (PFS) is descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits are presented. For each MM-398-containing arm, PFS is compared to the control arm. Hypothesis tests are

conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment are considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI are calculated for each treatment arm. For each MM-398-containing arm, ORR is compared to the control arm. Differences in objective response rate between each MM-398-containing arm and control arm are provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, are used to compare objective response rates.

The maximum reduction (% change from baseline) in CA19-9 is computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses is carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement is considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline are included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response is estimated, along with corresponding 95% confidence intervals, by treatment arm.

Overall Survival (OS) is the time from randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS is descriptively summarized for each arm using Kaplan-Meier methodology. For each MM-398-containing arm, OS is compared to the control arm. Hypothesis tests are conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

<u>Quality of Life Analyses</u>

Quality of life analyses are performed using patients in the analysis populations for each quality of life instrument (EORTC-QLC-C30, EQ-5D-5L). EORTC-QLQ-30 and EQ-5D-5L results will be summarized at each visit by treatment group

For each EORTC QLQ-C30 administered, scores are computed for the following scales: Global Health Status, Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial difficulties.

Scoring is carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations are applied to the raw scores so that the reported score will have range 0-100 for all scales. Summary statistics are presented for each subscale. A summary health state index value is computed for each EQ-5D-5L assessment. Summary statistics are presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses are tabulated.

Safety Analysis

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events are reported by the MedDRA version 17.1 or higher. Toxicity is graded according to the NCI CTCAE version 4.03.

Safety analysis of patients in Part 1 is to include a summary of dose-limiting toxicity events.

The period for treatment-emergent adverse events and safety findings is from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event is then considered as treatment-emergent.

Tabular summaries are to be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events are

to be summarized by System Organ Class and preferred term. All adverse event data is to be listed by patient.

Laboratory data is presented by cycle. Abnormal laboratory values are assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data are reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) are assessed. Shift to most severe toxicity grade are summarized.

Vital signs and ECG are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Vital signs are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Biomarker Subgroup Analysis

Analyses are performed to assess the associations between potential biomarkers (from plasma and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays are performed when appropriate.

Pharmacokinetics Analysis

Plasma concentrations of MM-398 and oxaliplatin can be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients can be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated (MM-398) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), are used to examine any possible interactions between MM-398 and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. NONMEM®, Version 7.3, is used to estimate individual PK parameters and simulate plasma exposures.

Example 4: Tolerability of Antineoplastic Therapies in Human Clinical Trial

The tolerability of antineoplastic therapies combining liposomal irinotecan, 5-FU/leucovorin and oxaliplatin was evaluated in a human clinical trial described in Example 3, using two different doses: 80 mg/m^2 (salt) of liposomal irinotecan (MM-398) and 60 mg/m^2 (salt) of liposomal irinotecan (MM-398). Table 15 summarizes three dosing regimens for the treatment of previously untreated (front-line) pancreatic cancer in humans over a 28 day treatment cycle.

Table 15 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
1	60	1, 15	2400/400	1, 15	80	1, 15
2	85	1, 15	2400/400	1, 15	80	1, 15
-2A[d]	75	1, 15	2400/400	1, 15	80	1, 15

a First dose administration in conjunction with first dose of nal-IRI; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle
Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

Initially, a combination of oxaliplatin, MM-398 liposomal irinotecan, leucovorin and 5-fluorouracil at dose level 1 in Table 15 above. The results are summarized in Table 16 for dose level 1 in Table 15 above (for 80 mg/m^2 (salt) M-398 dose), showing that the 80 mg/m^2 (salt) dose of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin at dose level 1 was not tolerated in humans.

Table 16: Antineoplastic Therapy with 80 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 3 Day 15
1	✓	✓	X	X	X	X

2	✓	R	R	R	X	X
3	✓	X	X	X	X	X
4	✓	✓	X	X	X	X
5	✓	X	X	X	X	X
6	✓	✓	R	R	R	R
7	✓	X	X	X	X	X

Table 16 summarizes the results from treating a total of seven (7) patients as part of Part 1 of Arm 1 shown in Figure 12. All seven patients met the applicable inclusion criteria specified below, including a diagnosis of pancreatic cancer.

A "check mark" (✓) in Table 16 indicates the patient received the antineoplastic therapy of dose level 1 in Table 15 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R" in Table 16 indicates the patient received a reduced dose of antineoplastic therapy of dose level -1 in Table 2 (Example 3 above) on the corresponding cycle and day: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

An "X" in Table 16 indicates the patient did not receive an antineoplastic therapy combining liposomal irinotecan, oxaliplatin, 5-fluorouracil and leucovorin or combining liposomal irinotecan, oxaliplatin, and 5-fluorouracil. After cycle 1, day 1 and prior to cycle 1, day 15, patient 2 was determined to be homozygous for the UGT1A1*28 allele, and subsequent reduced doses of the antineoplastic therapy were administered on days indicated in Table 16, based on the protocol of Example 3. Patients 1 and 3-7 were not homozygous for UGT1A1*28 allele.

The antineoplastic therapy of dose level 1 in Table 15 (Example 4) was only administered to 2 of these 6 patients on day 15 of (28-day) cycle 1, no patients received dose level 1 for more than 2 consecutive doses, and none of the patients received this therapy after cycle 1.

Accordingly, as noted in the Table 16, antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin were not well tolerated in a human clinical trial (resulting in dose limiting toxicities). Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 15.

In contrast, as noted in Table 18 below, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m2 of 5-fluorouracil and (l+d) leucovorin were tolerated in a human clinical trial. In particular, dose level -1 in Table 17 (a 60 mg/m^2 (salt) M-398 dose) was administered two or more consecutive times to multiple human patients in the clinical trial described in Example 3. These antineoplastic therapies comprising the reduced 60 mg/m^2 (salt) of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin were better tolerated in humans than dose level 1 in Table 15. In other embodiments, patients are administered the therapy of dose level -2B in Table 17.

Table 17 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Table 18: Antineoplastic Therapy with 60 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1
1	✓	✓	R2	R2	R2
2	✓	✓	✓		
3	✓	✓	✓		
4	✓	✓			
5	✓	✓	✓		

Table 18 summarizes the results from treating a total of five (5) patients as part of Part 1 of Arm 1 shown in Figure 12. All five patients met the applicable inclusion criteria specified in Example 3, including a diagnosis of pancreatic cancer. A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

In contrast to the antineoplastic therapy of dose level 1 in Table 14, the antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered repeatedly to patients 2 and 6 for at least 3 consecutive administrations (including 4 consecutive administrations for patient 6).

The antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered to 5 of 5 patients on days 1 and 15 of (28-day) cycle 1, and days 1 and 15 of (28 day) to 3 of 4 patients in the study, with no dose limiting toxicities. The antineoplastic therapy of dose level -1 was administered repeatedly to all 5 patients for at least 2 consecutive administrations.

A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding

amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R2" in Table 18 indicates the patient received a reduced dose of antineoplastic therapy of dose on the corresponding cycle and day: 50 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 1,800 mg/m^2 5-fluorouracil (a 25% reduction compared to dose level -1 dose), as described in the protocol of Example 3. One patient in Table 18 received this reduced dose in response to Grade II symptoms (non-hematologic), but without a dose limiting toxicity.

Accordingly, as noted in the Table 18, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin were well tolerated in a human clinical trial. Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 17.

Example 5: ONIVYDE® (irinotecan liposome injection) Liposomal Irinotecan

One preferred example of an irinotecan liposome described herein is the product marketed as ONIVYDE® (irinotecan liposome injection). ONIVYDE® is a topoisomerase inhibitor, formulated with irinotecan in a liposomal dispersion, for intravenous use.

The finished ONIVYDE® product is a white to slightly yellow opaque sterile concentrate for infusion. It consists of an isotonic dispersion of liposomes containing irinotecan hydrochloride trihydrate. The liposomes are small unilamellar lipid bilayer vesicles, approximately 110 nm in diameter, enclosing an aqueous compartment that contains irinotecan in a gelated or precipitated state, as sucrosofate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES)

as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL. The liposomes are dispersed in an aqueous buffered solution.

The ONIVYDE® product contains irinotecan sucrosofate encapsulated in a liposome, obtained from an irinotecan hydrochloride trihydrate starting material. The chemical name of irinotecan is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. The dosage of ONIVYDE® can be calculated based on the equivalent amount of irinotecan trihydrate hydrochloride starting material used to prepare the irinotecan liposomes, or based on the amount of irinotecan in the liposome. There are about 866 mg of irinotecan per gram of irinotecan trihydrate hydrochloride. For example, an ONIVYDE® dose of 80 mg based on the amount of irinotecan hydrochloride trihydrate starting material actually contains about 0.866x(80mg) of irinotecan in the final product (i.e., a dose of 80 mg/m^2 of ONIVYDE® based on the weight of irinotecan hydrochloride starting material is clinically equivalent to about 70 mg/m^2 of irinotecan in the final product). Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL.

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FEE TRANSMITTAL

Complete if known	
Application Number	TBD
Filing Date	November 10, 2017
First Named Inventor	Eliel BAYEVER
Examiner Name	TBD
Art Unit	TBD
Practitioner Docket No.	263266-421428

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 1,600.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 503145 Deposit Account Name: Honigman Miller Schwartz and Cohn LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☐ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☐ Credit any overpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	280	140*	70	600	300	150	720	360	180	1,600.00
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
20	-20 or HP =		x		=	

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
3	-3 or HP =		x		=	

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Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

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Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
84	- 100 =		/ 50 =	(round up to a whole number)	x		=	

4. OTHER FEE(S) — Fees Paid ($)

Non-English specification, $130 fee (no small or micro entity discount)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)

Other (e.g., late filing surcharge): _____

SUBMITTED BY

Signature	/Cynthia M. Bott/	Registration No. (Attorney/Agent) 46,568	Telephone 734-418-4280
Name (Print/Type)	Cynthia M. Bott, Ph.D.		Date November 10, 2017

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/809,815	11/10/2017	1629	1600	263266-421428	20	3

CONFIRMATION NO. 5137

FILING RECEIPT

139696
Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

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Date Mailed: 12/15/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

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Power of Attorney: The patent practitioners associated with Customer Number 139696

Domestic Priority data as claimed by applicant

This application is a CON of 15/241,106 08/19/2016
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and claims benefit of 62/273,244 12/30/2015
and claims benefit of 62/216,736 09/10/2015
and claims benefit of 62/208,209 08/21/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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If Required, Foreign Filing License Granted: 12/13/2017
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/809,815**
Projected Publication Date: 03/22/2018
Non-Publication Request: No
Early Publication Request: No
Title

Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/809,815

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

To: patents@honigman.com,lzerby@honigman.com,arhoades@honigman.com
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 139696

Dec 15, 2017 05:02:38 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15809815	APP.FILE.REC	12/15/2017	263266-421428

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U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with Customer Number: 153749

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

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	Address			
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Assignee Name and Address: IPSEN BIOPHARM LTD.
Ash Road, Wrexham Industrial Estate
Wrexham LL13 9UF, Great Britain

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Janice M. Klunder	Date	26-Feb-2018
Name	Janice M. Klunder	Telephone	617-679-8530
Title	Vice President, Head of Global Intellectual Property, IPSEN BIOPHARM LTD.		

Electronic Acknowledgement Receipt

EFS ID:	31913572
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	139696
Filer:	Deborah Marion Sharfman/Charity Dunn
Filer Authorized By:	Deborah Marion Sharfman
Attorney Docket Number:	263266-421428
Receipt Date:	28-FEB-2018
Filing Date:	10-NOV-2017
Time Stamp:	12:18:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73	2018-02-28_01208-0007-01US_373Statement.pdf	120255 fa6ce0960a1cffdef09b32a8e63bf58ac414ab60	no	3

Warnings:

Information:					
2	Power of Attorney	Ipsen_POA_AIA.pdf	957770 63d8a2c91f50021a5c83dc7c83bfdc3521afe2a7	no	1

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New International Application Filed with the USPTO as a Receiving Office

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Ipsen Biopharm Ltd.

Application No./Patent No.: 15/809,815 Filed/Issue Date: November 10, 2017

Titled: METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

Ipsen Biopharm Ltd., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

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2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

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B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Eliel Bayever, Sarah F. Blanchette, Jonathan Basil Fitzgerald, Daniel F. Gaddy, Bart S. Hendriks, Helen Lee, Ashis To: Merrimack Pharmaceuticals, Inc.

   The document was recorded in the United States Patent and Trademark Office at
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2. From: Merrimack Pharmaceuticals, Inc. To: Ipsen Biopharm Ltd.

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STATEMENT UNDER 37 CFR 3.73(c)

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6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Deborah M. Herzfeld/	February 28, 2018
Signature	Date
Deborah M. Herzfeld	52,211
Printed or Typed Name	Title or Registration Number

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/809,815	11/10/2017	Eliel Bayever	263266-421428

CONFIRMATION NO. 5137

POWER OF ATTORNEY NOTICE

139696
Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

OC00000097789793

Date Mailed: 03/05/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2018.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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/agizaw/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/809,815	11/10/2017	Eliel Bayever	263266-421428

CONFIRMATION NO. 5137

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POA ACCEPTANCE LETTER

OC00000097789817

Date Mailed: 03/05/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

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/agizaw/

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8 December 2015 (08.12.2015)

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62/089,685 9 December 2014 (09.12.2014) US

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Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

WO 2016/094402 A1

(54) Title: TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN

(57) Abstract: Provided are methods for treating breast cancer in a patient by administering effective amounts of liposomal irinotecan sucrosofate (MM-398). The breast cancer may be triple negative breast cancer (TNBC), estrogen receptor/progesterone receptor (ER/PR) positive breast cancer, ER-positive breast cancer, or PR-positive breast cancer, or metastatic breast cancer.

TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/089,685, filed December 9, 2014, the entire contents of which are incorporated herein by reference in their entirety.

BACKGROUND

Irinotecan (also known as CPT-11) is a highly effective chemotherapeutic agent that, in the form of irinotecan hydrochloride, was approved nearly 20 years ago for the treatment of colorectal cancer. Irinotecan is an active prodrug that is converted in a much more active metabolite known as SN-38 by the action of a carboxylesterase enzyme. In tumors, this carboxylesterase activity is locally concentrated in tumor associated macrophages (TAMs).

MM-398 is a novel liposomally encapsulated preparation of irinotecan sucrosofate. The MM-398 nanoliposomal delivery system is designed to reduce systemic exposure and increase drug accumulation within tumors through the enhanced permeability and retention effect that results from the disorganized and leaky characteristics of tumor vasculature. MM-398 liposomes have been engineered with the aim of optimally exploiting the propensity of TAMs to take up liposomes and to thereby maximize activation of irinotecan to yield intratumoral SN-38. These factors contribute to altering systemic exposure and distribution of MM-398 as compared to irinotecan hydrochloride. Accordingly, safe and effective dosing of MM-398 is not the same as, and its side effect profile differs from that of irinotecan hydrochloride. The altered systemic exposure and distribution of MM-398 is designed to provide an opportunity to administer irinotecan therapy to cancer patients for whom irinotecan hydrochloride cannot be safely dosed in amounts required to provide effective therapy.

One group of cancer patients who would benefit from safe and effective dosing of irinotecan is breast cancer patents, for whom irinotecan hydrochloride has not proven adequately safe and effective to be approved for routine use. The present disclosure provides uses, dosing and administration parameters, methods of use and other factors for treating breast cancer with MM-398, and thereby address the need for new, effective treatments for breast cancer, and provides additional benefits.

SUMMARY

Provided are methods for treating breast cancer in a patient, the methods comprising administering to the patient liposomal irinotecan (for example, irinotecan sucrose octasulfate salt

liposome injection, also referred to as nal-IRI, PEP02, MM-398, or ONIVYDE) according to a particular clinical dosage regimen. Provided too is the use of MM-398 for the safe and effective treatment of breast cancer. Compositions adapted for use in such methods are also provided.

In one aspect, a method for treatment (*i.e.*, effective treatment) of a breast cancer tumor, in a patient (in other words, a use of MM-398) is provided, the method (or use) comprising: administering to the patient an effective amount of liposomal irinotecan in the form of MM-398. In one embodiment, the breast cancer is: a) HER2 negative breast cancer, or b) HER2 negative metastatic breast cancer, or c) HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion. In one embodiment, the brain lesion is a progressive brain lesion. In another embodiment, the administration is carried out in at least one cycle, wherein the cycle is a period of 2 weeks and the irinotecan is administered once per cycle on day 1 of each cycle, and wherein for at least a first cycle the irinotecan is administered at a dose of at least 60 mg/m^2 or at least 80 mg/m^2. In one embodiment, the dose is 80 mg/m^2. In another embodiment, at least the first cycle the irinotecan is administered at a dose of 80, 100, 120, 150, 180, 210, or 240 mg/m^2. In a particular embodiment, at least the first cycle the irinotecan is administered at a dose of 80 mg/m^2.

In one embodiment, the administration is carried out in at least two cycles and, if the patient is positive (homozygous) for the UGT1A1*28 allele, the dose following the first cycle is 20 mg/m^2 or 40 mg/m^2 lower than the dose given in the first cycle and if the patient is negative for the UGT1A1*28 allele, the dose following the first cycle is the same as the dose given in the first cycle. In another embodiment, all administrations following the first cycle are at the same dose.

In one embodiment, the breast cancer is triple negative or basal-like breast cancer. In another embodiment, the breast cancer is ER-positive, PR-positive, or ER/PR-positive breast cancer. In yet another embodiment, the breast cancer is metastatic breast cancer. In another embodiment, the patient does not have any brain lesions and the breast cancer is HER2 0+ or 1+ by immunohistochemistry, HER2 negative by *in situ* hybridization, or HER2 negative by dual-probe *in situ* hybridization. In another embodiment, prior to each administration of the irinotecan, the patient is pre-medicated with either or both of 1) dexamethasone and 2) either a 5-HT3 antagonist or another anti-emetic. In one embodiment, the irinotecan is administered intravenously over 90 minutes. In another embodiment, the administration of the irinotecan, an effective amount of at least one anti-cancer agent other than irinotecan is co-administered to the patient.

In one embodiment, the treatment results in a positive outcome in the patient. In one embodiment, the positive outcome is partial complete response (pCR), complete response (CR),

partial response (PR), or stable disease (SD). In another embodiment, the positive outcome is a reduction in: a) tumor size, b) tumor infiltration into peripheral organs, c) tumor metastasis or d) recurrence of tumor. In one embodiment, prior to treatment with the irinotecan, the patient receives a ferumoxytol infusion followed by an MRI scan.

In another aspect is provided a kit for treating a breast cancer in a human patient, the kit comprising a container holding 1) a second container holding at least one dose of MM-398 and 2) instructions for using the irinotecan according to the methods and uses disclosed herein.

DETAILED DESCRIPTION

I. Definitions

As used herein, a "patient" is a human cancer patient.

As used herein, "effective treatment" refers to treatment producing a beneficial effect, *e.g.*, amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer. Effective treatment may refer to alleviation of at least one symptom of a cancer. Such effective treatment may, *e.g.*, reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.

The term "effective amount" refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may do any one or any combination of (i) through (vii) as follows: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

The terms "co-administration," "co-administered," "concomitant administration" or minor variations of these terms, indicate administration of at least two therapeutic agents to a patient either simultaneously or sequentially within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (*e.g.*, per hour, per day, per week, per month, etc.) to a patient. Such parameters include, *e.g.*, the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, *e.g.*, taken at a single administration, *e.g.*, orally (*e.g.*, as one, two, three or more pills, capsules, etc.) or injected (*e.g.*, as a bolus). Dosage sizes may also relate to doses that are administered continuously (*e.g.*, as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

"Liposomal Irinotecan" refers to a formulation of the chemotherapy drug irinotecan wherein the irinotecan is encapsulated within a phospholipid bilayer. Examples of liposomal irinotecan include, for example, MM-398 (Merrimack Pharmaceuticals, Inc.) and IHL-305 (Yakult Honsha Co., LTD.).

As used herein, "cancer" refers to a condition characterized by abnormal, unregulated, malignant cell growth. In one embodiment, the cancer is pathologically characterized by a solid tumor, *e.g.*, a breast cancer, *e.g.*, triple negative breast cancer (TNBC, i.e., a breast cancer that is estrogen receptor negative and progesterone receptor negative and HER2 negative), estrogen receptor/progesterone receptor (ER/PR) positive breast cancer, ER-positive breast cancer, or PR-positive breast cancer, or metastatic breast cancer. As used herein, "tumor" and "lesion" are used interchangeably.

The terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent. Examples of a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

FERAHEME (ferumoxytol) is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is

17-31 nm in diameter. The chemical formula of ferumoxytol is $Fe_{5874}O_{8752}C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa. An iron replacement product, ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.

FERAHEME is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). The recommended dose of FERAHEME for this indication is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. In this context FERAHEME is administered as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). The dosage is expressed in terms of mg of elemental iron, with each mL of FERAHEME containing 30 mg of elemental iron. The hematologic response (hemoglobin, ferritin, iron and transferrin saturation) should be evaluated at least one month following the second FERAHEME injection. The recommended FERAHEME dose may be re-administered to patients with persistent or recurrent iron deficiency anemia. For patients receiving hemodialysis, administer FERAHEME once the blood pressure is stable and the patient has completed at least one hour of hemodialysis. The patient is monitored for signs and symptoms of hypotension following each FERAHEME injection. FERAHEME is contraindicated in patients with evidence of iron overload, known hypersensitivity to FERAHEME or any of its components, and anemia not caused by iron deficiency.

Administration of FERAHEME may transiently affect the diagnostic ability of magnetic resonance (MR) imaging. Anticipated MR imaging studies should be conducted prior to the administration of FERAHEME. Alteration of MR imaging studies may persist for up to 3 months following the last FERAHEME dose. If MR imaging is required within 3 months after FERAHEME administration, T1- or proton density-weighted MR pulse sequences should be used to minimize the FERAHEME effects; MR imaging using T2-weighted pulse sequences should not be performed earlier than 4 weeks after the administration of FERAHEME. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 – 2 days following FERAHEME administration. FERAHEME will not interfere with X-ray, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound or nuclear medicine imaging.

Although not an approved indication, ferumoxytol is currently being investigated as an imaging agent for the visualization of TAMs and tumor vasculature in cancer patients. Such imaging methods are disclosed, *e.g.*, in co-pending International Publication No. WO2014/113167.

II. Irinotecan sucrosofate liposome injection (MM-398)

MM-398 is a stable liposomal formulation of irinotecan sucrosofate (irinotecan sucrose octasulfate salt). MM-398 is typically provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of MM-398 may be diluted, *e.g.*, in 500 mL of 5% dextrose injection USP and infused over a 90 minute period. Additional information on the preparation and use of liposomal irinotecan sucrosofate can be found, *e.g.*, in United States patents 8,147,867 and 8,658,203, as well as in WIPO International Application No. PCT/US2013/045495.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules.

This stable liposomal formulation of irinotecan has several attributes designed to provide an improved therapeutic index. The controlled and sustained release improves activity by increasing duration of exposure of tumor tissue to irinotecan and SN-38. The long circulating pharmacokinetics of MM-398 and its high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR is believed to promote deposition of liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised, resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure within the tumor.

III. Irinotecan glucuronidation

The enzyme produced by the UGT1A1 gene, UDP-glucuronosyltransferase 1, is responsible for bilirubin metabolism and also mediates SN-38 glucuronidation, which is the initial step in the predominant metabolic clearance pathway of this active metabolite of irinotecan. Besides its anti-tumor activity, SN-38 is also responsible for the severe toxicity sometimes associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form, SN-38 glucuronide, is an important step in the modulation of irinotecan toxicity.

Mutational polymorphisms in the promoter of the UGT1A1 gene have been described in which there is a variable number of thymine adenine (ta) repeats. Promoters containing seven thymine adenine (ta) repeats (found in the UGT1A1*28 allele) have been found to be less active than the wild-type promoter (which has six repeats), resulting in reduced expression of UDP-glucuronosyltransferase 1. Patients who carry two deficient alleles of UGT1A1 exhibit reduced glucuronidation of SN-38.

The metabolic transformation of the irinotecan encapsulated in MM-398 to SN-38 includes two critical steps: (1) the release of the irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. The genetic polymorphisms in humans predictive for the toxicity of irinotecan and those of MM-398 can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance and longer elimination half-life of SN-38 of the MM-398 formulation compared to free irinotecan, the deficient genetic polymorphisms may show more association with severe adverse events and/or efficacy.

IV. Administration

MM-398 is administered by intravenous (IV) infusion over 90 minutes at, *e.g.*, a dose of 80 mg/m^2 every two weeks in patients not carrying the UGT1A1*28 allele. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days. As used herein, the dose of MM-398 refers to the dose of irinotecan based on the molecular weight of irinotecan hydrochloride trihydrate unless clearly indicated otherwise.

The dose may also be expressed as the irinotecan free base. Converting a dose based on irinotecan hydrochloride trihydrate to a dose based on irinotecan free base is accomplished by multiplying the dose based on irinotecan hydrochloride trihydrate with the ratio of the molecular weight of irinotecan free base (586.68 g/mol) and the molecular weight of irinotecan hydrochloride trihydrate (677.19 g/mol). This ratio is 0.87 which can be used as a conversion factor. For example, the 80 mg/m^2 dose based on irinotecan hydrochloride trihydrate is equivalent to a 69.60 mg/m^2 dose based on irinotecan free base (80 x 0.87). In the clinic this is rounded to 70 mg/m^2 to minimize any potential dosing errors. Similarly, a 120 mg/m^2 dose of irinotecan hydrochloride trihydrate is equivalent to 100 mg/ m^2 of irinotecan free base.

V. Patient Populations

In one embodiment, a patient treated using the methods and compositions disclosed herein has exhibited evidence of recurrent or persistent breast cancer following primary chemotherapy.

In another embodiment, the patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

The compositions and methods disclosed herein are useful for the treatment of all breast cancers, including breast cancers that are refractory or resistant to other anti-cancer treatments.

VI. Outcomes

Provided herein are methods for treating breast cancer in a patient, comprising administering to the patient liposomal irinotecan (MM-398) according to a particular clinical dosage regimen.

Responses to therapy may include:

Pathologic complete response (pCR): absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

Partial Response (PR): At least a 30% decrease in the sum of dimensions of target lesions, taking as reference the baseline sum diameters;

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) denotes at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression;

In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of a breast cancer.

In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number

of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as $\geq$10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target sites comprising lesions, *e.g.*, pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In some embodiments, administration of effective amounts of liposomal irinotecan according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a breast tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate (CBR = CR+ PR+ SD $\geq$ 6 months) better than that achieved by the same combinations of anti-cancer agents administered without concomitant MM-398 administration. In other embodiments, the improvement of clinical benefit rate is about 20% 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to the same combinations of anti-cancer agents administered without concomitant MM-398 administration.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1: Treatment Protocols

A. Study Design

A clinical trial will enroll patients with metastatic breast cancer in 3 cohorts:

Cohort 1: ER-positive, and PR-positive, or ER/PR-positive breast cancer

Cohort 2: TNBC

Cohort 3: Breast cancer with active brain metastasis

There are five stages to this study:

1 Screening (-28 d): Patients undergo screening assessments to determine if they are eligible for the study.

2 Ferumoxytol (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required MRI (Fe-MRI) scans and pre-treatment biopsy (if applicable, see Cohort requirements) prior to receiving MM-398.

3 MM-398 Treatment (C1D1 – progression of disease): Patients receive an MM-398 dose of 80 mg/m^2 every 2 weeks and other required assessments.

4 Follow up (+30 days from last dose): patients return to clinic 30 days following the last dose of MM-398 for final safety assessments MM-398 will be administered at a dose of 80 mg/m^2 every two weeks and patients will be treated until disease progression or unacceptable toxicity.

5 Overall survival period: Overall survival (OS) will be collected every month once patients are off study.

B. Patient Selection and Discontinuation

Up to 30 evaluable patients will be enrolled in this study.

I. Inclusion Criteria: In order to be included in the study, patients must have/be:

a) Pathologically confirmed solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy.

1. The following invasive breast cancer tumor sub-types are required:

i. Cohorts 1 and 2 must be documented to be HER2 negative as outlined in the ASCO/CAP 2013 guidelines for HER2 testing, defined by at least one of the following:

• HER2 immunohistochemistry (IHC) staining of 0 or 1+,

OR if HER2 IHC 2+

• Negative by *in situ* hybridization (ISH) based on defined as a single-probe average HER2 copy number of less than 4.0 signals/cell.

• OR Negative by Dual-probe ISH defined as a HER2/CEP17 ratio of greater than 2.0 with an average HER2 copy number of fewer than 4.0 signals/cell.

ii. In addition, patients must be able to be categorized into one of the following cohorts:

- Cohort 1: hormone receptor positive breast cancer patients with ER-positive and/or PR-positive tumors defined as ≥1% of tumor nuclei that are immunoreactive for ER- and/or PR- and HER2-negative
- Cohort 2: triple negative breast cancer (TNBC) patients with ER-negative, PR-negative tumors defined as < 1% of tumor nuclei that are immunoreactive for ER and PR and HER2 negative.
- Cohort 3: Any sub-type of metastatic breast cancer and active brain metastases (see additional criteria below).

b) Documented metastatic disease with at least two radiologically measurable lesions as defined by RECIST v1.1 (Eur. J. Cancer 45 (2009) 228-247) (except Cohort 3, see inclusion criteria below)

c) ECOG performance status 0 or 1

d) Bone marrow reserves as evidenced by:

- ANC > 1,500 cells/μl without the use of hematopoietic growth factors
- Platelet count > 100,000 cells/μl
- Hemoglobin > 9 g/dL

e) Adequate hepatic function as evidenced by:

- Normal serum total bilirubin
- AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present)

f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN

g) Normal ECG or ECG without any clinically significant findings

h) Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy

i) At least 18 years of age

j) Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Expansion Phase additional inclusion criteria:

k) Received at least one cytotoxic therapy in the metastatic setting, with exception of TNBC patients who progressed within 12 months of adjuvant therapy

l) Received ≤ 3 prior lines of chemotherapy in the metastatic setting (no limit to prior lines of hormonal therapy in Cohort 1)

m) Candidate for chemotherapy

n) At least one lesion amenable to multiple pass core biopsy (with the exception of Cohort 3)

The criteria for enrollment must be followed explicitly. Patients will be discontinued from the study treatment in the following circumstances:

Expansion Phase Cohort 3 additional inclusion criteria:

o) Radiographic evidence of new or progressive brain metastases after prior radiation therapy with at least one brain metastasis measuring ≥ 1 cm in longest diameter on gadolinium-enhanced MRI (note: progressive brain lesions are not required to meet RECIST v 1.1 criteria in order to be eligible; extra-cranial metastatic disease is also allowed)

p) Imaging following prior radiation is not consistent with pseudo-progression in the judgment of the treating clinician

q) Neurologically stable as defined by:

- Stable or decreasing dose of steroids and anti-convulsants for at least 7 days prior to study entry
- No clinically significant mass effect, hemorrhage, midline shift, or impending herniation on baseline brain imaging
- No significant focal neurologic signs and/or symptoms which would necessitate radiation therapy or surgical decompression, in the judgment of the treating clinician

r) No evidence of diffuse leptomeningeal disease on brain MRI or by previously documented cerebrospinal fluid (CSF) cytology-NOTE: discrete dural metastases are permitted.

II. Exclusion Criteria: Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

a) Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)

b) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1

c) Have received irinotecan or bevacizumab (or other anti-VEGF therapy) therapy within the last six months; and for Expansion Phase patients, have received any prior treatment with a Topo1 inhibitor (irinotecan-derived or topotecan)

d) History of any second malignancy in the last 3 years; patients with prior history of *in situ* cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years.

e) Unable to undergo MRI due to presence of errant metal, cardiac pacemakers, pain pumps or other MRI incompatible devices.

f) A history of allergic reactions to compounds similar to ferumoxytol, as described in full prescribing information for ferumoxytol injection, parenteral iron, dextran, iron-dextran, or parenteral iron-polysaccharide preparations

g) Known hypersensitivity to any of the components of MM-398, or other liposomal products

h) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease.

- Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

i) Active infection or an unexplained fever greater than 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome

j) Prior chemotherapy administered within three weeks, or within a time interval less than five half-lives of the agent, whichever is longer, prior to the first scheduled day of dosing in this study

k) Received radiation therapy in the last 14 days

l) Evidence of iron overload as determined by:

- Fasting transferrin saturation of >45 % and/or
- Serum ferritin levels >1000 ng /ml

m) Treated with iron supplements in the previous four weeks

n) HIV-positive patients on combination antiretroviral therapy or other conditions requiring treatment where there is a potential for ferumoxytol to have a negative pharmacokinetic interactions

o) Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, to cooperate, and to participate in the study, or to interfere with the interpretation of the results

p) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a reliable method of birth control, during the study and for 3 months following the last dose of study drug.

C. Patient Discontinuation

Patients may withdraw or be withdrawn from the study at any time and for any reason. Some possible reasons for early withdrawal include, but are not limited to the following:

- Progressive neoplastic disease
- The patient experiences an adverse event which, in the opinion of the Investigator, precludes further participation in the trial.
- Clinical and/or symptomatic deterioration
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Noncompliance with the protocol
- Withdraws consent
- The Investigator removes the patient from the trial in the best interests of the patient
- Study termination by the Sponsor
- Use of prohibited concomitant medications
- Lost to follow up

If a patient withdraws from the trial, attempts should be made to contact the patient to determine the reason(s) for discontinuation. All procedures and evaluations required by the 30 day follow up visit should be completed when a patient is discontinued. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event.

D. Description and Use of MM-398

MM-398 is supplied as sterile, single-use vials containing 9.5 mL of MM-398 at a concentration of 5 mg/mL. The vials contain a 0.5 mL excess to facilitate the withdrawal of the label amount from each 10 mL vial.

MM-398 must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. MM-398 must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe.

MM-398 must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 6 hours if kept at room temperature (15-30°C).

Twenty vials of MM-398 will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

Dosage and Administration

In one embodiment, MM-398 is dosed and administered as follows.

MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of 80 mg/m^2 every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) to a final volume of 500 mL. Care should be taken not to use in-line filters or any diluents other than D5W. MM-398 can be administered at a rate of up to 1 mL/sec (30 mg/sec) using standard PVC-containing intravenous administration bags and tubing.

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

E. Important Treatment Considerations with MM-398

Data from previous MM-398 studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the treatment procedures for managing those toxicities are provided below.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of MM-398, prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide. Loss of fluids and electrolytes

associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia, with discretion. Patients, who are known to have experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan- containing regimens; the specific cause of these events has not been determined.

Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

Care of Intravenous Site

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended.

Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion-Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

Other Toxicity Potential

MM-398, the new liposome formulation of irinotecan, is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

F. Dose Modification Requirements

Dosing may be held for up to 2 weeks from an occurrence, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 2 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Grade 1: Transient flushing or rash, drug fever <38° C (<100.4° F); intervention not indicated

Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs

Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension

Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1

Slow infusion rate by 50%

Monitor patient every 15 minutes for worsening of condition

Grade 2

Stop infusion

Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen

Resume infusion at 50% of the prior rate once infusion reaction has resolved

Monitor patient every 15 minutes for worsening of condition

For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 25-50 mg IV

Grade 3

Stop infusion and disconnect infusion tubing from patient

Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary

No further treatment with MM-398 will be permitted

Grade 4

Stop the infusion and disconnect infusion tubing from patient

Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm

Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV

Consider hospital admission for observation

No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

G. MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table 1: MM-398 Dose Modifications for Neutrophil Count

Worst CTCAE Grade	ANC Levels (cells/mm^3)	Modification
Grade 1 or 2	1000 – 1999	Same as previous dose
Grade 3 or 4	<1000	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.

Table 2: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	Modification
< Grade 2	Same as previous dose
Grade 3 or 4	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.

H. MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below.

Table 3: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	Description	Modification
Grade 1	2-3 stools/day > pretreatment	Same as previous dose
Grade 2	4-6 stools/day > pretreatment	Same as previous dose
Grade 3	7-9 stools/day > pretreatment	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.
Grade 4	>10 stools/day > pretreatment	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.

Table 4: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia

Worst Toxicity CTCAE Grade	Modification
Grade 1 or 2	Same as previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy and reduce dose to 60 mg/m^2; if the patient is already receiving, for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.

I. Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

Antiemetic Medications

Dexamethasone and a 5-HT3 blocker (*e.g.*, ondansetron or granisetron) will be administered to all patients as premedications unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.

Colony Stimulating Factors

Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever; prophylactic use of G-CSF will be permitted only in those

patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy or have had documented grade 3 or 4 neutropenia or neutropenic fever while receiving prior anti-neoplastic therapy.

Therapy for Diarrhea

Acute diarrhea and abdominal cramps, developing during or within 24 hours after MM-398 administration, may occur as part of a cholinergic syndrome. The syndrome will be treated with atropine. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms during the study.

Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea are abstracted below.

Table 5: Management of Chemotherapy Induced Diarrhea

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

The synthetic octapeptide octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 micrograms twice daily to 500 micrograms three times daily, with a maximum tolerated dose of 2000 micrograms three times daily in a 5-day regimen. Patients should be advised to drink water copiously throughout treatment.

Other Treatments

Symptomatic treatment for other toxicities should be per institutional guidelines. Prevention of alopecia with cold cap or of stomatitis with iced mouth rinses is allowed.

I. Prohibited Therapy

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any other that interact with irinotecan, should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the country specific package inserts of 5-FU and leucovorin for any other drug interactions.

The following therapies are not permitted during the trial:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy; palliative radiotherapy is permitted; and
- Any other investigational therapy is not permitted.

J. Laboratory Procedures

Complete Blood Count

A complete blood count (CBC) will be performed locally, and must include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

Serum Chemistry

Serum chemistry panel will be performed centrally. Additionally, chemistry may also be assessed locally, and local lab results may be used for enrollment and treatment decisions, if central lab results are not available. If local lab results are used for enrollment, then local lab results must be used for all subsequent treatment decisions. Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

Biomarker Samples

Whole blood and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to MM-398, and MM-398 PK. Non-limiting examples of potential analyses include cytokine levels (*e.g.*, MCSF1 and IL-6), growth factors (*e.g.*, IGF-1 and EGFR family receptors and ligands), and enzyme levels (*e.g.*, MMP9).

Coagulation Profile

A coagulation profile will include a partial thromboplastin time and an international normalized ratio.

UGT1A1*28 Allele

A whole blood sample will be collected from all patients at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of MM-398, but subsequent doses of MM-398 may be reduced for patients positive (homozygous) for the UGT1A1*28 allele,

Urine or Serum Pregnancy Test

All women of child bearing potential must undergo a urine or serum pregnancy test.

Pharmacokinetic Assessments

Plasma samples will be collected to determine the levels of MM-398 and SN-38. Additional analytes which may impact the pharmacokinetics of MM-398 may also be measured from this sample. The PK time points outlined in Table 13 below will be drawn during Cycles 1-3.

Table 6: Summary of PK Time-points in Treatment and Follow-up Phases

Sample	Time-point (Cycles 1-3)	Window
1	Immediately prior to MM-398 infusion on Day 1	-5 minutes
2	At the end of the MM-398 infusion	+5 minutes
3	+2 hours after the completion of the MM-398 infusion	+/- 30 minutes
4	+ 48 hours after the completion of the MM-398 infusion	+/- 24 hours
5	+168 hours/7 days after the completion of the MM-398 infusion	+/- 24 hours
6	Immediately prior to MM-398 infusion on D15	- 24 hours
7	30 day follow up visit	----

K. Pain Assessment and Analgesic Consumption

Pain assessment and analgesic consumption diaries will be provided to the patients for recording their pain intensity daily on a visual analogue scale and to document their daily analgesic use.

L. EORTC-QLQ-C30

Quality of life will be assessed by the EORTC-QLQ-C30 instrument. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included.

Patients will be required to complete the EORTC-QLQ-C30 questionnaire at time points outlined in the Schedule of Assessment. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients, for whom validated translations of the EORTC-QLQ-C30 questionnaire are available, will be required to complete the questionnaire.

M. Overall Survival/Post Study Follow-up

Overall survival data will be collected after a patient completes the 30 day follow-up visit, every 1 month (+/- 1 week) from the date of the 30 day follow-up visit. Post-discontinuation data to be collected will include: the date of disease progression (if not already documented; if patient discontinued from study treatment for reasons other than objective disease progression, patient should continue to undergo tumor assessment every 6 weeks, until commencement of new anti-neoplastic therapy or progressive disease); documentation of any anticancer treatment patient has received including the dates of any post-discontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. All patients must be followed-up until death or study closure, whichever occurs first.

N. Determining the Severity and Relatedness of Adverse Events

Each adverse event will be graded according to the NCI CTCAE V 4.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal, which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event
- **Fatal**: an event that results in the death of the patient

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

O. Efficacy Analyses

Progression Free Survival

PFS is defined as the number of months from the date of randomization to the date of death or progression, whichever occurred earlier (per RECIST 1.1). If neither death nor progression is observed during the study, PFS data will be censored at the last valid tumor assessment.

PFS will be compared between the treatment groups using paired un-stratified log-rank tests. The PFS curves will be estimated using Kaplan-Meier estimates. Estimates of the hazard ratios and corresponding 95% confidence intervals will be obtained using Cox proportional hazard models. Stratified analyses will also be carried out using the randomization stratification factors. Treatment effects adjusting for stratification variables and other prognostic covariates will be explored. In addition, different censoring and missing data imputing methods may be used to perform sensitivity analyses on PFS. Methodology for the sensitivity analyses will be fully specified in the Statistical Analysis Plan.

The analyses will be performed for ITT, PP and EP populations.

Time to Treatment Failure

Time to treatment failure is defined as time from randomization to either disease progression, death or study discontinuation due to toxicity. Kaplan-Meier analyses as specified for analyses of progression free survival will be performed for time to treatment failure. The analyses will be performed for ITT, PP and EP populations.

Objective Response Rate

The tumor assessment related to ORR will be determined using RECIST v1.1. If the Sponsor requires an independent review of the radiological assessments to support a new drug application or for any other reason, the response status of all patients may be reviewed by an independent panel of clinicians and may be reviewed by the Sponsor or its designee. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment will take precedence.

Objective response rate (ORR) for each treatment group will be calculated combining the number of patients with a best overall response of confirmed CR or PR per RECIST v 1.1. The ORR is the best response recorded from randomization until progression or end of study. The number and percentage of patients experiencing objective response (confirmed CR + PR) at the time of analysis will be presented and the 95% confidence interval for the proportion will be calculated. Objective response rates from the treatment arms will be compared using pair-wise Fisher's Exact Tests. The analyses will be performed for ITT, PP and EP populations.

Tumor Marker Response Analysis

CA 19-9 serum levels will be measured within 7 days before the start of treatment (baseline), and subsequently every 6 weeks. Tumor marker response of CA19-9 will be evaluated by the change of CA19-9 serum levels. Response is defined as a decrease of 50% of CA 19-9 in relation to the baseline level at least once during the treatment period. Only patients with elevated baseline CA 19-9 value (> 30 U/mL) will be included in the calculation of tumor marker response rate.

Patient Reported Outcome Analyses

Analysis of the EORTC-QLQ-C30 questionnaires will be performed in accordance with the EORTC guidelines [22].

Safety Analysis

Treatment emergent adverse events will be presented by treatment arm, by patient, by NCI CTCAE grade and by MedDRA system organ class (SOC). Separate listings will be presented for total adverse events, serious adverse events, adverse events related to the study drugs and Grade 3 and 4 adverse events. Laboratory data will be presented by treatment arm and by visit. Abnormal laboratory values will be assessed according to NCI CTCAE grade, where possible. Evaluation of QTc will be done based upon Fridericia's correction method. CTCAE criteria will be applied to the QTc_F (i.e. Grade 3 = QTc > 500 msec). All the safety analyses will be performed by treatment arm, treatment cycle and week, where appropriate. Overall safety will also be evaluated by grade across cycles, SOC and extent of exposure. Additionally, safety analyses will include a comparison between the treatment arms in all patients in the Safety Population:

- Number of blood transfusions required
- Proportion of patients requiring G-CSF
- Adverse events resulting in dose delay or modification

Pharmacokinetics Analysis

Pharmacokinetic data will be collected on all patients randomized to either of the MM-398 arms. Plasma concentration-time data for MM-398 will be analyzed using population pharmacokinetic methods. Pharmacokinetic parameters will be estimated by Non-Linear Mixed Effects Modeling using NONMEM®, Version 7, Level 1.0 (ICON Development Solutions, Dublin, Ireland). PK parameters will include plasma C_{max}, T_{max}, AUC (area under the concentration curve), clearance, volume of distribution, and terminal elimination half-life. The effects of patient specific factors (age, race, gender, body weight, hepatic and renal function measures, ECOG value, etc.) on pharmacokinetic parameters will be evaluated. Population

PK/PD methods will be used to assess the relationships between drug exposure and efficacy and/or toxicity (*e.g.* neutropenia, diarrhea) parameters.

Additional exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study. Concentration levels of 5-FU will be summarized descriptively.

Example 2: Ferumoxytol Magnetic Resonance Imaging

It is anticipated that the MRI parameters will need to be optimized in patients that are enrolled at the beginning of the study and/or in the Expansion Phase, in order to assess any correlations between Fe-MRI signal and TAMs, pharmacodynamic markers, or tumor response. Each patient will be required to complete their Fe-MRIs on the same scanner to reduce inter-scan variability. Each MRI study will be evaluated for image quality and signal characteristics of tumors and reference tissue on T1-, T2- and T2*- weighted sequences. Once a completed set of images from each patient has been received, the images will be loaded onto the viewing workstation for qualitative review and then sent to a quantitative lab for analysis.

During the Expansion Phase, multiple MR images will be collected on Day 1-Day 2 of the ferumoxytol period, at various time points depending on the scan group to which the patient is assigned. The body areas to be scanned will be determined by the location of the patient's disease; detailed instructions are described in the study imaging manual. All patients will have a baseline image acquired prior to the ferumoxytol infusion, and either a second successive image (baseline repeat; Scan Group 1) or a second image occurring 1-4 h after the end of ferumoxytol administration (Scan Groups 2 and 3). All patients will return on Day 2 for a 24 h Fe-MRI using the same protocol and sequences as on Day 1. Patients enrolled into Scan Groups 1 and 2 will require one additional scan either at 24 h or 2 weeks, for a total of 4 scans. Patients will be assigned in an alternating fashion to Scan Groups 1 and 2 before enrollment into Scan Group 3 begins.

Table 7: Scan groups and required time points

Scan group	N[a]	Baseline	Baseline (repeat)	1-4 hours	24 hours	24 hours (repeat)	2 week Baseline
1	5	X	X		X		X
2	5	X		X	X	X	
3	10	X		X	X		

a. Enrollment into Scan Groups 1 and 2 may be increased at the discretion of the Sponsor, in the event that any of the images are not evaluable, or it is determined that more information is

needed from the additional scan time points. In this case, enrollment into Scan Group 3 will be decreased by a corresponding number of patients.

Table 8: Fe-MRI schedule for Cohort 3 patients with active brain metastases:

Scan group	N	Baseline	Baseline (repeat)	1-4 hours	24 hours	24 hours (repeat)	2 week Baseline
Cohort 3	10	X[a]		X[b]	X[a]		

a. Patients with extra-cranial disease will have MRIs of two body areas at baseline and 24 hours: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease).

b. Brain scan only will be completed at this time point

Administration of ferumoxytol (FERAHEME)

A single dose of ferumoxytol will be administered at Day 1 by intravenous infusion. Dosing is calculated according to patient weight at 5 mg/kg. The total single dose will not exceed 510 mg, the maximum approved single dose of ferumoxytol. Ferumoxytol has in the past been administered as an undiluted IV injection at a rate of up to 1 ml/sec (30 mg/second), with monitoring of vital signs. Alternatively, and in order to mitigate the risk of any toxicity associated with the bolus injection of ferumoxytol, all enrolled patients will receive a single dose of 5 mg/kg of ferumoxytol at Day 1 during the ferumoxytol period by intravenous infusion in 50-200 mL of 0.9% sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution.

This dosing schedule is less intense than the approved label, which recommends two doses of 510 mg 3 to 8 days apart; however since the use of ferumoxytol as disclosed herein is as an imaging agent, as opposed to a replacement product for iron deficiency, a lower dose is more appropriate.

Ferumoxytol is administered while the patient is in a reclined or semi-reclined position. Patients are closely monitored for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during administration and for at least 30 minutes following each infusion as per the ferumoxytol label instructions.

Important considerations when administering ferumoxytol

Iron levels will be measured in the blood prior to ferumoxytol administration. As currently recommended by the American Association of Liver Disease, screening for iron overload is diagnosed by measuring a fasting morning transferrin saturation $\geq$ 45% (ratio of serum iron divided by the serum total iron binding capacity and expressed as a percentage). A ferritin level of 1000 ng/ml is likely to be also associated with organ damaging levels of iron. Both

measurement of transferrin saturation and serum ferritin can be altered by inflammation as occurs in malignancy, and may be difficult to interpret. Actual tissue measurement of liver iron is the gold standard for diagnosing iron overload but is associated with some morbidity. Careful interpretation of iron test, preferably by an expert, is recommended.

Example 3: Physical, Chemical, and Pharmaceutical Properties of MM-398

Drug Product

The MM-398 drug product contains the drug substance irinotecan in the amount equivalent to 5 mg/mL of irinotecan hydrochloride trihydrate. The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as the sucrosofate salt. The liposome carriers are composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 6.81 mg/mL; cholesterol, 2.22 mg/mL; and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidylethanolamine (MPEG-2000-DSPE), 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer, 4.05 mg/mL; sodium chloride as isotonicity reagent, 8.42 mg/mL; and sucrose octasulfate as the drug trapping agent, 0.9 mg/mL. The solution is buffered at pH 7.25. In the vialed product, greater than 98% of the drug is encapsulated in the liposome carrier. MM-398 Injection is supplied as a sterile solution containing 5.0 mg/ml of irinotecan hydrochloride encapsulated in liposomes. The appearance of MM-398 is white to slightly yellow opaque liquid.

Description and List of Excipients

Table 14 below shows the composition of MM-398 Injection, 5.0 mg/ml drug product. Drug product composition for the 10 mL solution in the vial is also included.

Table 14: Quantitative Composition of MM-398 Injection, 5.0 mg/ml

Component	Concentration mg/mL	mg/vial (10 mL)
Irinotecan, hydrochloride, trihydrate	5.0	50
Distearoyl phosphatidylcholine (DSPC)	7.9	79
Cholesterol	2.6	26
Pegylated (MW: 2000) Distearoyl phosphatidylethanolamine (PEG 2000 DSPE)	0.14	1.4
Sodium chloride	7.9	79
N-2-Hydroxyethylpiperazine-N'-2- ethanesulfonic acid (HEPES)	4.8	48
Sodium hydroxide	q.s. to target pH to 6.5	q.s. to target pH to 6.5
Water for Injection	q.s. to 1.0 ml	q.s. to 10.0 ml

Abbreviations: MW = molecular weight; q.s. = add sufficient quantity.
Note: DSPC : Cholesterol : PEG 2000 DSPE = 3 : 2 : 0.015 (molar ratio)

Storage Conditions and Shelf Life

Prior to administration, MM-398 Injection must be diluted in 5% Dextrose Injection or Normal Saline (0.9% Sodium Chloride Injection) to a suitable volume for infusion. The solution for infusion (MM-398 Injection and its admixtures) must not be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan. Because of the potential for microbial contamination during dilution, the solution for infusion should be used immediately, but may be stored at room temperature (15° to 30°C) for up to 4 hours prior to the start of the infusion. If necessary, the solution for infusion may be refrigerated (2° to 8°C) for no more than 24 hours prior to use. MM-398 has been tested for compatibility with limited materials, and no compatibility issues have been identified. The following materials were tested:

- Infusion sets (without in- line filter) made of PVC or polyethylene lined
- IV bags made of PVC or coextruded film of polyolefin/polyamide
- MM-398 drug product must be stored at 2°C to 8°C.

Adventitious Agents Safety Evaluation

The only component of biological origin in MM-398 is cholesterol, which is derived from sheep wool. Manufacture of MM-398 uses cholesterol exclusively derived from sheep in New Zealand, where BSE/TSE has not been reported. This material is in compliance with the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products {EMA/410/01 Rev. 3 - March 2011) adopted by the EU Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal products (CVMP). The MM-398 cGMP manufacturing process extensively controls for reduction and minimization of bioburden throughout and the drug product is sterile filtered prior to aseptic filling into vials. Product in-process and final testing assures sterility of MM 398.

Pharmacokinetics and Drug Metabolism in Humans

The pharmacokinetics of MM-398 was evaluated using sample-rich and sparse PK sampling across 6 studies (Study PEP0201, Study PEP0203, Study PEP0206, Study PIST-CRC-01, Study MM-398-01-01-02, and Study MM-398-07-03-01). Both non-compartmental analysis and population pharmacokinetic analysis were performed to evaluate the pharmacokinetic properties of MM-398.

Pharmacokinetic Parameters

A summary of PK parameters from non-compartmental analysis is provided in Table 2 below.

Table 2: Summary Statistics of MM-398 NCA Parameters across Multiple PK Studies

PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max} [µg/ml or ng/ml]‡	80	25	38.0	36	25	4.7	89
	120	45	59.4	41	45	7.2	57
$t_{1/2}$ [h]	80	23†	26.8	110	13†	49.3	103
	120	45	15.6	198	40†	57.4	67
$AUC_{0-\infty}$ [h·µg/ml or h·ng/ml]‡	80	23†	1030	169	13†	587	69
	120	45	1258	192	40†	574	64
V_d [L/m^2]	80	23†	2.2	55	NA	NA	NA
	120	45	1.9	52	NA	NA	NA

†$t_{1/2}$ and $AUC_{0-\infty}$ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available. C_{max} are in µg/ml for total irinotecan and ng/ml for SN-38; AUC are in h µg/ml for total irinotecan and h ng/ml for SN-38.

Population Pharmacokinetics

Population pharmacokinetic analysis was performed for total irinotecan and SN-38 in 353 patients across 6 studies to identify major sources of inter-patient variability and to establish MM-398 exposure-response relationship. The SN-38 originating from the in vivo conversion of released irinotecan was predicted from the model and denoted as "SN-38 Converted".

From the population pharmacokinetic analysis, total irinotecan was approximately 3 orders of magnitude higher than SN-38. Compared to 120 mg/m^2 q3w, doses of 80 mg/m^2 q2w MM-398 resulted in similar average concentration, 1.5-fold lower C_{max} of both irinotecan and SN-38, and 7-fold higher SN-38 Converted C_{min}.

Endnotes

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known

or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein.

Those skilled in the art will recognize, or be able to ascertain and implement using no more than routine experimentation, many equivalents of the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

Any combinations of the embodiments disclosed in the various dependent claims are contemplated to be within the scope of the disclosure.

The disclosure of each and every U.S., international, or other patent or patent application or publication referred to hereinabove is incorporated herein by reference in its entirety.

What is claimed is:

1. A method of treatment of a breast cancer in a human patient, the method comprising: administering to the patient an effective amount of liposomal irinotecan, wherein the breast cancer is: a) HER2 negative metastatic breast cancer, or b) HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion.

2. The method of claim 1, wherein the administration is carried out in at least one cycle, wherein the cycle is a period of 2 weeks and the irinotecan is administered once per cycle on day 1 of each cycle, and wherein for at least a first cycle the liposomal irinotecan is administered at a dose of at least 60 mg/m^2 or at least 80 mg/m^2.

3. The method of claim 2, wherein for at least the first cycle the liposomal irinotecan is administered at a dose of 80, 100, 120, 150, 180, 210, or 240 mg/m^2.

4. The method of claim 2 or claim 3, wherein for at least the first cycle the liposomal irinotecan is administered at a dose of 80 mg/m^2.

5. The method of any one of claims 1-4 wherein the administration is carried out in at least two cycles and, if the patient is homozygous for the UGT1A1*28 allele, the dose following the first cycle is 20 mg/m^2 or 40 mg/m^2 lower than the dose given in the first cycle and if the patient is not homozygous for the UGT1A1*28 allele, the dose following the first cycle is the same as the dose given in the first cycle.

6. The method of any one of claims 1-5, wherein all administrations following the first cycle are at the same dose.

7. The method of any one of claims 1-6, wherein the breast cancer is triple negative or basal-like breast cancer.

8. The method of any one of claims 1-6, wherein the breast cancer is ER/PR positive breast cancer.

9. The method of any one of claims 1-8, wherein the breast cancer is HER2 negative metastatic breast cancer.

10. The method of any one of claims 1-8, wherein the breast cancer is HER2 negative or HER2 positive metastatic breast cancer with at least one brain lesion and wherein the at least one brain lesion is a progressive lesion.

11. The method of any one of claims 1-9, wherein the patient does not have any brain lesions and the breast cancer is HER2 0+ or 1+ by immunohistochemistry, HER2 negative by *in situ* hybridization, or HER2 negative by dual-probe *in situ* hybridization.

12. The method of any one of claims 1-11, wherein, prior to each administration of the liposomal irinotecan, the patient is pre-medicated with either or both of 1) dexamethasone and 2) either a 5-HT3 antagonist or another anti-emetic..

13. The method of any one of claims 1-12, wherein the liposomal irinotecan is administered intravenously over 90 minutes

14. The method of any one of claims 1-13, wherein, concomitant with the administration of the liposomal irinotecan, an effective amount of at least one anti-cancer agent other than irinotecan is co-administered to the patient.

15. The method of any one of claims 1-14, wherein the treatment results in a positive outcome in the patient.

16. The method of claim 15, wherein the positive outcome is pCR, CR, PR, or SD.

17. The method of claim 15, wherein the positive outcome is a reduction in: a) the number of cancer cells, b) tumor size, c) infiltration into peripheral organs, d) tumor metastasis or e) recurrence of tumor.

18. The method of any one of claims 1-17, wherein, prior to treatment with the liposomal irinotecan, the patient receives a ferumoxytol infusion followed by an MRI scan.

19. The method of any one of claims 1-17, wherein the liposomal irinotecan is MM-398.

20. A kit for treating a breast cancer in a human patient, the kit comprising a container holding 1) a second container holding at least one dose of liposomal irinotecan and 2) instructions for using the liposomal irinotecan according to the method of any one of claims 1-18.

21. The kit according to claim 20, wherein the liposomal irinotecan is MM-398.

AMENDED CLAIMS
received by the International Bureau on 13 May 2016 (13.05.2016)

What is claimed is:

1. Use of a single dose of 80 mg/m^2 of liposomal irinotecan administered once every two weeks for the treatment of breast cancer in a human patient following the administration of a dose of ferumoxytol to the human patient.

2. The method of claim 1, wherein the administration of the dose of ferumoxytol is followed by obtaining an image of the ferumoxytol in the patient prior to administration of the liposomal irinotecan and wherein the image is obtained with an MRI scan.

3. The method of claim 3, wherein the body areas scanned are determined by the location of the patient's lesion.

4. The use of claim 3, wherein the ferumoxytol is detected in a breast cancer lesion and the breast cancer lesion is selected from the group consisting of: a hormone receptor positive breast cancer lesion, an ER-positive lesion, a PR-positive lesion, a ER-positive/ PR-positive lesion, triple negative breast cancer lesion, a metastatic breast cancer lesion and an active brain metastatic lesion.

5. The use of anyone of claims 1-4, wherein the breast cancer lesion is a metastatic breast cancer lesion.

6 The use of claim 5, wherein the breast cancer lesion is an active brain metastatic lesion.

7. The use of any one of claims 1-6, wherein the human patient is not homozygous for the UGT1A1*28 allele.

8. The use of any one of claims 1-7, wherein the dose is a single dose of 5 mg/kg up to a total single dose that does not exceed 510 mg.

9. The use of anyone of claims 2-8, wherein the image is obtained 1-4 hours after the administration of the ferumoxytol.

10. The use of anyone of claims 2-8, wherein the image is obtained 24 hours after the administration of the ferumoxytol.

11. The use of any one of claims 1-10, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in a liposome.

STATEMENT UNDER ARTICLE 19(1)

Claims 1-21 have been canceled. The basis for new claims 1-11 is provided below.

(i) Basis for new claim 1: The basis for this claim can be found in original claim 4 and on page 10, lines 9-10, and page 15, lines 6-7, of the specification as filed.

(ii) Basis for new claim 2: The basis for this claim can be found page 10, lines 1-10, and claim 18, of the specification as filed.

(iii) Basis for new claim 3: The basis for this claim can be found on page 28, lines 17-18, of the specification as filed.

(iv) Basis for new claim 4: The basis for this claim can be found on page 11, lines 3-10, and the abstract of the specification as filed.

(v) Basis for new claim 5: The basis for this claim can be found on page 11, lines 9-10, of the specification as filed.

(vi) Basis for new claim 6: The basis for this claim can be found in Table 8 and on page 11, line9, of the specification as filed.

(vii) Basis for new claim 7: The basis for this claim can be found on page 7, lines 15-16, and in original claim 5, line 4 of the claim (as dependent from claim 4).

(ix) Basis for new claim 8: The basis for this claim can be found on page 29, lines 10-11.

(x) Basis for new claim 9: The basis for this claim can be found on page 28, tables 7 and 9, in the specification as originally filed.

(xi) Basis for new claim 10: The basis for this claim can be found on page 28, tables 7 and 8, in the specification as originally filed.

(xii) Basis for new claim 11: The basis for this claim can be found on page 1 line 32 through page 2, line 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/064491

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/436 A61K9/127 A61K35/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFREY R INFANTE ET AL: "Phase I and pharmacokinetic study of IHL-305 (PEGylated liposomal irinotecan) in patients with advanced solid tumors", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 70, no. 5, 2 September 2012 (2012-09-02), pages 699-705, XP035132528, ISSN: 1432-0843, DOI: 10.1007/S00280-012-1960-5	20
Y	page 702	1-21

X	WO 2014/113167 A1 (MERRIMACK PHARMACEUTICALS INC [US]) 24 July 2014 (2014-07-24)	20,21
Y	claim 15	1-21

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2016	19/02/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Steendijk, Martin

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/064491

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/030864 A1 (NEOPHARM INC [US]; RAHMAN AQUILUR [US]; AHMAD IMRAN [US]) 17 April 2003 (2003-04-17)	20,21
Y	page 6; claim 1	1-21
X	US 2007/110798 A1 (DRUMMOND DARYL C [US] ET AL) 17 May 2007 (2007-05-17)	20,21
Y	page 25; claims; example 10	1-21
Y	HIDETOSHI HAYASHI ET AL: "Phase II study of bi-weekly irinotecan for patients with previously treated HER2-negative metastatic breast cancer: KMBOG0610B", BREAST CANCER, vol. 20, no. 2, 29 November 2011 (2011-11-29), pages 131-136, XP055246819, JP ISSN: 1340-6868, DOI: 10.1007/s12282-011-0316-z abstract	1-21
Y	WO 2012/012454 A1 (BIPAR SCIENCES INC [US]; BRADLEY CHARLES [US]) 26 January 2012 (2012-01-26) claims	1-21
A	WO 2013/188586 A1 (MERRIMACK PHARMACEUTICALS INC [US]) 19 December 2013 (2013-12-19) claims	1-21
X,P	Anonymous: "Abstract P5-01-06: Characterization of metastatic breast cancer lesions with ferumoxytol MRI and treatment response to MM-398, nanoliposomal irinotecan (nal-IRI)", , 1 May 2015 (2015-05-01), XP55245815, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/75/9_Supplement/P5-01-06 [retrieved on 2016-01-28] abstract	1-21

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/064491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014113167 A1	24-07-2014	AU 2013374248 A1	11-06-2015
		US 2014170075 A1	19-06-2014
		WO 2014113167 A1	24-07-2014
WO 03030864 A1	17-04-2003	US 2005019387 A1	27-01-2005
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		CA 2875824 A1	19-12-2013
		CN 104717961 A	17-06-2015
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		KR 20150021565 A	02-03-2015
		US 2015182521 A1	02-07-2015
		US 2015328156 A1	19-11-2015
		US 2015374682 A1	31-12-2015
		WO 2013188586 A1	19-12-2013

Notice of References Cited	Application/Control No. 15/809,815	Applicant(s)/Patent Under Reexamination Bayever et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO-2013-188586	12-2013		Bayever et al	
	O	WO-2016-094402	06-2016		Bayever et al	
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Conroy T Folfirinox versus gemcitabine for metastatic pancreatic cancer, nejm, 34(19), 2011, 1817
	V	Fleming D, http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/ 2014
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	263266-421428	5137

153749 7590 03/06/2018

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EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/06/2018	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 15/809,815	Applicant(s) Bayever et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10 November 2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED CORRESPONDENCE

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 5-8, 10, 16 and 19 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Bayever et al disclosed a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan). Bayever further disclosed 5-fluorouracil at a dose of 2400 mg/m^2 and leucovorin (/ form

administered at 200 mg/m^2 or the l+d racemic form administered at 400 mg/m^2). The method comprised at least one cycle of administration, wherein the cycle was a period of two weeks (page 3, last full paragraph).

In one embodiment, Bayever's population was patients undergoing treatment for metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10).

Bayever did not disclose oxaliplatin, as recited in claim 9.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro* (page 1818, left column, second paragraph).

Conroy did not disclose that the irinotecan was liposomal irinotecan.

Since Bayever disclosed treating metastatic pancreatic carcinoma with 5-fluorouracil and irinotecan, it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment. An ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy (Conroy, page 1818, left column, second paragraph).

The combination of Bayever and Conroy reads on claims 1, 16 and 19.

Claim 2 is rendered prima facie obvious because Bayever disclosed active agents administered at 60 mg/m^2 (e.g. irinotecan) once per two weeks, as discussed above.

Claim 3 is rendered prima facie obvious because Conroy disclosed 85 mg/m^2 oxlaliplatin (abstract). Bayever disclosed the administration of actives biweekly, as discussed above.

Claims 5-6 and 8 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes, and that leucovorin was administered prior to 5-FU (page 12, section IV).

Claim 7 is rendered prima facie obvious because Bayever disclosed that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle), because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Bayever disclosed irinotecan sucrose octasulfate liposomal irinotecan, where the irinotecan was entrapped within the liposome, at page 4, and the last paragraph.

Claims 4, 9 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and

further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy has been discussed above.

Additionally, Bayever disclosed that prior to each administration of liposomal irinotecan, the patient was pre-medicated with dexamethasone (e.g. corticosteroid) and another anti-emetic (page 4, fourth embodiment from the top of the page).

Further, Conroy disclosed that a second active agent was given two hours after a first active agent (e.g., leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose oxaliplatin administration after liposomal irinotecan, as recited in claims 4 and 18; liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming disclosed that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy disclosed administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration

was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration.

An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Claims 11-15, 17 and 20 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817), as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever (2013), in view of Conroy, has been discussed above.

Although, Bayever (2013) disclosed MM-398 liposome (at page 4, last paragraph and as discussed above), Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12, 17 and 20.

However, Bayever (2016) evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE (page 30, section describing the drug product).

Thus, it is reasonable to assume that Bayever's (2013) MM-398 contained irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.

Claims 13-15, 17 and 20 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes; liposomal irinotecan was administered prior to leucovorin; leucovorin was administered prior to 5-FU (page 12, section IV). Further, Bayever disclosed that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration.

For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28-day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Nonstatutory Double Patenting

A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 9,492,442, in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the method of

treatment except for the administration of oxlaliplatin. The instant claims require oxaliplatin, and such an ingredient is not recited by the issued claims.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro* (page 1818, left column, second paragraph).

Thus, it would have been prima facie obvious to have used oxaliplatin in the issued method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro.*

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/652,513, in view of Conroy et al (NEJM, 34(19), 2011, 1817).

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7 AM-5 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

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ABSTRACT

BACKGROUND

Data are lacking on the efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer.

METHODS

We randomly assigned 342 patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating a greater severity of illness) to receive FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at a dose of 1000 mg per square meter weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks. Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival.

RESULTS

The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001).

CONCLUSIONS

As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status. (Funded by the French government and others; ClinicalTrials.gov number, NCT00112658.)

From Nancy University and Centre Alexis Vautrin, Nancy (T.C.); Centre Léon Bérard, Lyon (F.D., C.F.); Centre Val d'Aurelle (M.Y., S.G.-B.) and Centre Hospitalo-Universitaire Saint-Eloi (E.A.), Montpellier; Centre Hospitalier Universitaire Robert Debré, Reims (O.B.); Institut Claudius Regaud, Toulouse (R.G.); Institut Bergonié, Bordeaux (Y.B.); Centre Oscar Lambret, Lille (A.A.); Centre Eugène Marquis, Rennes (J.-L.R.); Centre René Gauducheau, Nantes (J.B.); Hôpital Ambroise Paré, Boulogne-Billancourt (J.-B.B.); Centre Hospitalier, Perpignan (F.K.-A.); Hôpital de la Croix Rousse, Lyon (D.P.-V.); Centre Hospitalier Henri Mondor, Créteil (C.D.); Centre Georges-François Leclerc, Dijon (B.C.); Rouen University Hospital and University of Rouen, Rouen (P.M.); Unicancer–Bureau d'Etudes Cliniques et Thérapeutiques, Paris (C.M.-G.); Institut Gustave Roussy, Villejuif (M.D.); and Paris-Sud 11 University, Le Kremlin-Bicêtre (M.D.) — all in France. Address reprint requests to Dr. Conroy at the Department of Medical Oncology, Centre Alexis Vautrin, 54511 Vandoeuvre-lès-Nancy CEDEX, France, or at t.conroy@nancy.fnclcc.fr.

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Pancreatic adenocarcinoma was the fourth leading cause of death from cancer in the United States in 2010,[1] and it carries a grim prognosis: the 5-year survival rate is 6% in Europe and the United States.[1,2] Gemcitabine became the reference regimen for advanced pancreatic cancer after a randomized trial showed significant improvement in the median overall survival as compared with fluorouracil administered as an intravenous bolus (5.6 vs. 4.4 months, P=0.002).[3] In the subsequent phase 3 trials of single-agent gemcitabine,[4] the median overall survival ranged from 5.0 to 7.2 months. The combination of gemcitabine with a variety of cytotoxic and targeted agents has generally shown no significant survival advantage as compared with gemcitabine alone.[4] Some studies have suggested a significant benefit associated with gemcitabine-based cytotoxic combinations in patients with good performance status.[5-7]

Irinotecan has some clinical activity against advanced pancreatic cancer.[8,9] Preclinical studies have indicated that irinotecan has synergistic activity when it is administered before fluorouracil and leucovorin.[10-13] Oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil.[14] Oxaliplatin and irinotecan show synergistic activity in vitro.[15] Given the relative absence of overlapping toxic effects among fluorouracil, leucovorin, irinotecan, and oxaliplatin, a regimen combining these agents was studied in a phase 1 trial and showed responses in patients with advanced pancreatic cancer.[16] Accordingly, we conducted a phase 2 study of the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil, and leucovorin) involving 46 patients with good performance status and advanced pancreatic cancer; this regimen was associated with encouraging efficacy and grade 3 or 4 neutropenia in half the patients.[17] These results prompted the initiation of a phase 2-3 trial to further explore FOLFIRINOX as compared with single-agent gemcitabine as first-line treatment in patients with metastatic pancreatic cancer.

METHODS

PATIENTS

Patients were eligible to be included in the study if they were 18 years of age or older and had histologically and cytologically confirmed, measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature [e.g., light housework or office work])[18] and adequate bone marrow (granulocyte count, ≥1500 per cubic millimeter; and platelet count, ≥100,000 per cubic millimeter), liver function (bilirubin ≤1.5 times the upper limit of the normal range), and renal function.

Exclusion criteria were an age of 76 years or older, endocrine or acinar pancreatic carcinoma, previous radiotherapy for measurable lesions, cerebral metastases, a history of another major cancer, active infection, chronic diarrhea, a clinically significant history of cardiac disease, and pregnancy or breast-feeding.

STUDY DESIGN AND OVERSIGHT

This multicenter, randomized, phase 2–3 trial was conducted at 15 centers during phase 2 and expanded to 48 centers during phase 3. Patients were randomly assigned to receive FOLFIRINOX or gemcitabine within 1 week after enrollment. Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization (the head vs. the body or tail of the pancreas).

The study was approved by the Lorraine ethics committee. All patients provided written informed consent. An independent data and safety monitoring committee supervised the collation of efficacy and safety data. The trial was conducted according the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and relevant French and European laws and directives. The study was designed and the first draft of the manuscript was prepared by the first author, with writing assistance from an employee of the sponsor, Unicancer, and in cooperation with the other authors. Data were collected at the headquarters of the French anticancer centers (Unicancer, the study sponsor) and analyzed by the statistician, who vouches for the accuracy of the data. Oxaliplatin and irinotecan were donated by Sanofi-Aventis and Pfizer, respectively; these drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript.

The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The first author vouches for the fidelity of the study to the protocol.

TREATMENT

Gemcitabine, at a dose of 1000 mg per square meter of body-surface area, was delivered by 30-minute intravenous infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3 weeks in subsequent 4-week courses. FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg per square meter over a 46-hour period every 2 weeks. In the gemcitabine group, a cycle was also defined as a 2-week interval. Six months of chemotherapy was recommended for patients who had a response. Patients were followed every 3 months until death.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see the Supplementary Appendix, available at NEJM.org). Doses of gemcitabine were reduced by 25% if the granulocyte count decreased to 500 to 999 per cubic millimeter or if the platelet count was 50,000 to 100,000 per cubic millimeter. In case of grade 2, 3, or 4 neutropenia or thrombocytopenia, FOLFIRINOX administration was delayed until recovery and doses were reduced. Filgrastim was not recommended as primary prophylaxis, but it could be considered for high-risk patients.

ASSESSMENTS

At the start of every cycle, the patient's status was assessed according to his or her medical history, complete physical examination by a physician, ECOG performance status, and complete blood counts and blood chemical tests. Baseline evaluations also included measurement of the serum carbohydrate antigen 19-9 level, a computed tomographic (CT) evaluation, and assessment of the patient's quality of life with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30, version 3.0).[19]

EORTC QLQ-C30 questionnaires were to be completed every 2 weeks. Safety assessments were performed before each cycle with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[20] Tumors were measured every 2 months.

Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (see the Supplementary Appendix).[21] Independent review of CT scans was performed at the end of phase 2 of the study. Overall survival and progression-free survival were calculated from the date of randomization until the date of death and the date of documentation of disease progression or death in patients without disease progression, respectively.

STATISTICAL ANALYSIS

The primary efficacy end point for the phase 2 analysis was tumor response, and the secondary end point was safety. The trial was planned to continue as a phase 3 study if more than 11 responses were observed in the first 40 patients who were randomly assigned to the FOLFIRINOX group. Patients from the phase 2 analysis were included in the phase 3 analysis. The primary end point for the phase 3 analysis was overall survival. Secondary end points were progression-free survival, tumor response, safety, and quality of life. The statistical considerations are detailed in the Sample Size Determination section in the Supplementary Appendix.

All analyses were performed on an intention-to-treat basis. Qualitative variables were compared with the use of the chi-square test or Fisher's test, quantitative variables with the use of Student's t-test or a nonparametric (Wilcoxon) test, and survival data with the use of a stratified log-rank test. All these comparisons were adjusted for stratification factors. All tests were two-sided, with a P value of less than 0.05 considered to indicate statistical significance. Data are presented with 95% confidence intervals, calculated with the use of standard methods based on a binomial distribution. All analyses were performed with the use of Stata software, version 10.

Overall survival and progression-free survival were estimated with the use of the Kaplan–Meier method.[22] A Cox proportional-hazards model was

Table 1. Demographic and Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	FOLFIRINOX (N=171)	Gemcitabine (N=171)
Age — yr		
Median	61	61
Range	25–76	34–75
Sex — no. (%)		
Male	106 (62.0)	105 (61.4)
Female	65 (38.0)	66 (38.6)
ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
Pancreatic tumor location — no. (%)		
Head	67 (39.2)	63 (36.8)
Body	53 (31.0)	58 (33.9)
Tail	45 (26.3)	45 (26.3)
Multicentric	6 (3.5)	5 (2.9)
Biliary stent — no. (%)		
Yes	27 (15.8)	22 (12.9)
No	144 (84.2)	149 (87.1)
No. of metastatic sites involved		
Median	2	2
Range	1–6	1–6
Level of carbohydrate antigen 19-9 — no./total no. (%)		
Normal	24/164 (14.6)	23/165 (13.9)
Elevated, <59×ULN	72/164 (43.9)	65/165 (39.4)
Elevated, ≥59×ULN	68/164 (41.5)	77/165 (46.7)
Unknown	7/171 (4.1)	6/171 (3.5)
No. of measurable metastatic sites — no. of patients/total no. (%)		
Liver	149/170 (87.6)	150/171 (87.7)
Pancreas	90/170 (52.9)	91/171 (53.2)
Lymph node	49/170 (28.8)	39/171 (22.8)
Lung	33/170 (19.4)	49/171 (28.7)
Peritoneal	33/170 (19.4)	32/171 (18.7)
Other	18/170 (10.6)	29/171 (17.0)

* ECOG denotes Eastern Cooperative Oncology Group; FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin; and ULN upper limit of the normal range.

used to estimate the hazard ratios. Hazard ratios indicating the effects of prognostic factors on the risk of death were calculated and are shown in a forest plot.[23] The interaction test was used to assess the heterogeneity of treatment effects for subgroup analyses.[24]

Analysis of the QLQ-C30 questionnaires was performed in accordance with the EORTC guidelines.[25] The preplanned analysis centered on the scales that are usually most affected in patients with pancreatic cancer: the Global Health Status and Quality of Life scale and scales for fatigue, pain, physical functioning, emotional functioning, and role functioning.[26] The other QLQ-C30 domains were only examined in an exploratory manner. Time to definitive deterioration in quality of life, with the use of a 10-point minimal clinically important difference,[27,28] was analyzed with the use of the Kaplan–Meier method and the log-rank test.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between December 2005 and October 2009, a total of 342 patients from 48 French centers were enrolled in the study. The database was closed for final analysis on April 16, 2010. The intention-to-treat population included 171 patients in each group, and the safety population (all patients who received treatment) included 167 patients in the FOLFIRINOX group and 169 patients in the gemcitabine group (Fig. I in the Supplementary Appendix). There were similar numbers of patients with minor violations of eligibility criteria in the FOLFIRINOX and gemcitabine groups (8 and 7, respectively).

Demographic and baseline disease characteristics of the patients were similar in the two treatment groups (Table 1), but there were fewer measurable target lung metastases in the FOLFIRINOX group than in the gemcitabine group (19.5% vs. 28.7%, P=0.05).

The median number of treatment cycles administered was 10 (range, 1 to 47) in the FOLFIRINOX group and 6 (range, 1 to 26) in the gemcitabine group (P<0.001). More patients in the gemcitabine group had disease progression before 12 cycles (6 months) (79.9%, vs. 54.6% in the FOLFIRINOX group; P<0.001). The median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.

EFFICACY

Response to Therapy

A total of 88 patients were recruited between January 2005 and November 2006 during phase 2 of this study. The confirmed response rate, according to the investigators, was 31.8% (14 of 44 pa-

tients) in the FOLFIRINOX group and 11.3% (5 of 44 patients) in the gemcitabine group. Independent review confirmed an objective response rate of 34.1% (in 15 patients) in the FOLFIRINOX group. Since the primary objective of phase 2 was met, the trial proceeded to phase 3. All patients in phase 2 continued treatment, and data on these patients are fully reported in the phase 3 efficacy and safety results.

The response to therapy in the phase 3 trial is summarized in Table 2. The objective response rate was 31.6% (95% confidence interval [CI], 24.7 to 39.1) in the FOLFIRINOX group and 9.4% (95% CI, 5.4 to 14.7) in the gemcitabine group (P<0.001). In both groups, after 12 cycles, chemotherapy could be discontinued in patients with a response or stable disease; in 7.6% of the patients in the FOLFIRINOX group and 7.0% of those in the gemcitabine group, the same regimen was reintroduced with the use of a stop-and-go strategy.

Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

* CI denotes confidence interval, and FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin.
† The rate of objective response was defined as the percentage of patients who had a complete response or partial response.
‡ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease.

Survival

The median duration of follow-up was 26.6 months (95% CI, 20.5 to 44.9). The overall survival analysis was based on 273 deaths among the 342 patients (79.8%). The median overall survival was 11.1 months (95% CI, 9.0 to 13.1) in the FOLFIRINOX group as compared with 6.8 months (95% CI, 5.5 to 7.6) in the gemcitabine group (hazard ratio for death, 0.57; 95% CI, 0.45 to 0.73; P<0.001) (Fig. 1A). Overall survival rates at 6, 12, and 18 months were 75.9%, 48.4%, and 18.6%, respectively, in the FOLFIRINOX group as compared with 57.6%, 20.6%, and 6.0%, respectively, in the gemcitabine group.

Synchronous metastases, a low baseline albumin level (<3.5 g per deciliter), hepatic metastases, and an age of more than 65 years were identified as independent adverse prognostic factors for overall survival (see the Supplementary Appendix). The hazard ratio for death with FOLFIRINOX treatment, adjusted for these variables, was significant (adjusted hazard ratio, 0.54; 95% CI, 0.41 to 0.73; P<0.001). Results were similar when adjusted according to the presence or absence of pulmonary metastases. The effect of FOLFIRINOX was homogeneous in all subgroups (Fig. 2).

The analysis of progression-free survival was based on 317 events among 342 patients (92.7%). The median progression-free survival was 6.4 months (95% CI, 5.5 to 7.2) in the FOLFIRINOX group as compared with 3.3 months (95% CI, 2.2 to 3.6) in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001) (Fig. 1B). Progression-free survival rates at 6, 12, and 18 months were 52.8%, 12.1%, and 3.3%, respectively, in the FOLFIRINOX group as compared with 17.2%, 3.5%, and 0%, respectively, in the gemcitabine group.

SECOND-LINE THERAPY

Second-line therapy was administered in 80 patients in the FOLFIRINOX group and in 85 patients in the gemcitabine group. No difference in median survival was noted between the groups (4.4 months in each group) from the introduction of second-line therapy. The most common second-line regimens were as follows: in the FOLFIRINOX group, gemcitabine (in 82.5% of the patients) or a gemcitabine-based combination (in 12.5%), and in the gemcitabine group, a combination of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) (in 49.4%); gemcitabine plus oxaliplatin (in 17.6%); a regimen of fluorouracil and leucovorin plus cisplatin every 2 weeks (in 16.5%); and FOLFIRINOX (in 4.7%).

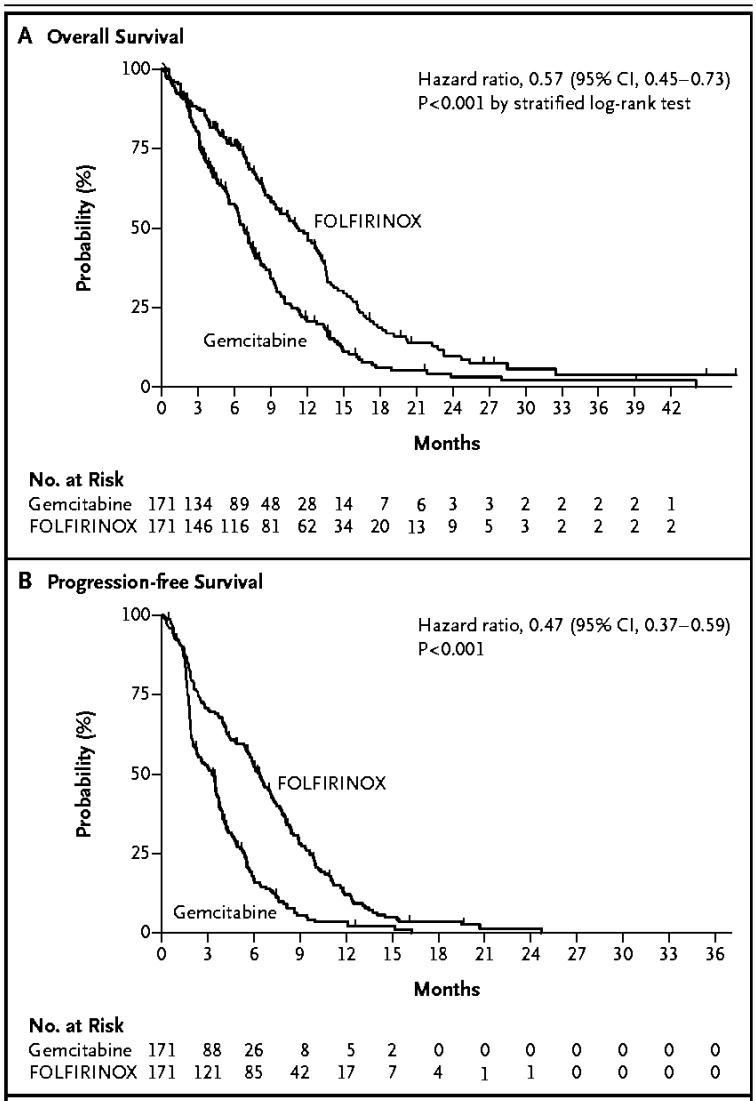

Figure 1. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival, According to Treatment Group.

Panel **A** shows overall survival; the median was 11.1 months in the group receiving FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). Panel B shows progression-free survival; the median was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group.

ADVERSE EVENTS

Two patients died from treatment-related cause: one from febrile neutropenia in the FOLFIRINOX group and one from cardiac decompensation in the gemcitabine group. Treatment-related grade 3 or 4 adverse events occurring in more than 5% of patients in either treatment group are summarized in Table 3. Incidences of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were significantly higher in the FOLFIRINOX group, whereas the incidence of grade 3 or 4 elevated alanine aminotransferase levels was significantly higher in the gemcitabine group. Grade 2 alopecia occurred in 11.4% of patients in the FOLFIRINOX group and in 1.2% of patients in the gemcitabine group (P<0.001). No cholangitis was observed. In both groups, the hematologic toxicity and the risk of infection were similar with or without placement of a biliary stent. Filgrastim was administered in 42.5% of patients who received FOLFIRINOX and in 5.3% of patients who received gemcitabine (P<0.001).

QUALITY OF LIFE

The proportion of patients with QLQ-C30 questionnaires that could be evaluated at baseline was 95.3% in the FOLFIRINOX group and 95.9% in the gemcitabine group. No significant differences between the groups were noted at baseline in the QLQ-C30 scales or single items. Subsequently, the rate of compliance with completion of the QLQ-C30 questionnaire was high: 78.2% in the FOLFIRINOX group and 77.4% in the gemcitabine group. No significant differences were noted between the groups in the Global Health Status and Quality of Life scale or in the individual domains, except that the FOLFIRINOX group had higher scores for diarrhea during the first eight cycles.

At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive decrease in the scores on the Global Health Status and Quality of Life scale versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001) (Fig. II in the Supplementary Appendix). Significant increases in the time until definitive deterioration in the quality of life were also noted in the FOLFIRINOX group for all functional and symptom scales and with respect to appetite loss, dyspnea, and constipation. Time to a definitive decrease in the scores that were associated with diarrhea, insomnia, or financial difficulties caused by a physical condition or medical treatment did not differ significantly between regimens.

DISCUSSION

In this study, FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status. The median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months).

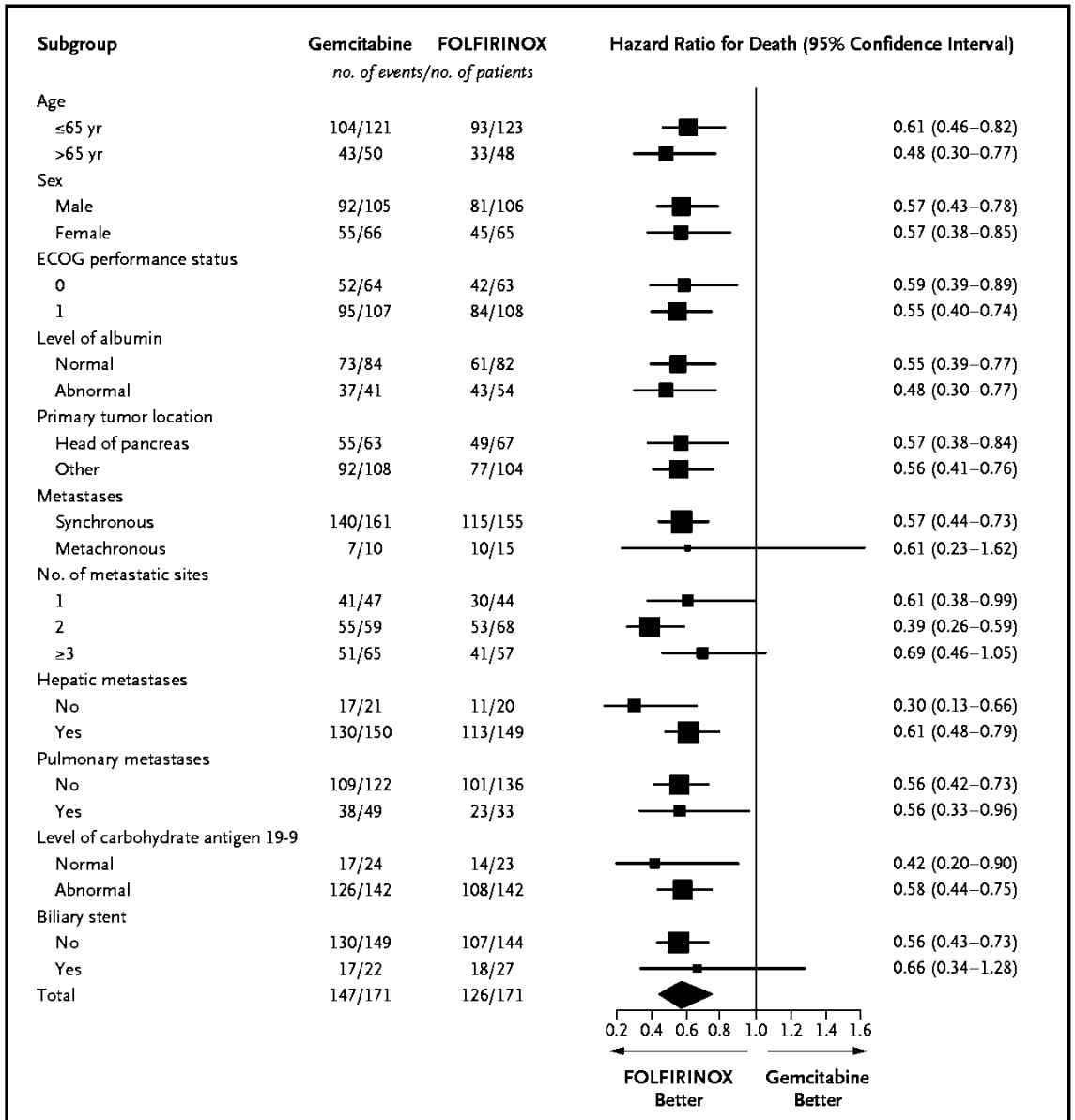

Figure 2. Forest Plot of the Treatment Effect on Overall Survival in Subgroup Analyses.

The Eastern Cooperative Oncology Group (ECOG) grades the status of patients with respect to activities of daily living, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work). The sizes of the squares are proportional to the sizes of the subgroups. Horizontal lines represent 95% confidence intervals. The position of each square represents the point estimate of the treatment effect.

Single-agent gemcitabine is the current standard of care,[4,29] but the addition of cytotoxic and targeted agents to gemcitabine has almost invariably provided no significant survival improvement,[4] despite an improvement in response rates in some trials.[30-34] Conversely, one phase 3 trial involving 569 patients with locally advanced or metastatic cancer showed a significant prolongation of overall survival with the combination of erlotinib and gemcitabine as compared with gemcitabine alone (hazard ratio for death, 0.82; 95% CI, 0.69 to 0.99; P=0.04). However, the magnitude of the improvement in median overall survival was modest, at 0.33 months (6.24 vs. 5.91 months).[35]

Recently, a phase 3 trial involving 543 patients with advanced pancreatic cancer showed that the combination of capecitabine and gemcitabine as

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N = 171)	Gemcitabine (N = 171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

compared with gemcitabine alone resulted in an increased response rate (19.1% vs. 12.4%, P=0.03) and improved progression-free survival (hazard ratio for disease progression, 0.78; 95% CI, 0.66 to 0.93; P=0.04), as well as a trend toward improvement in overall survival (hazard ratio for death, 0.86; 95% CI, 0.72 to 1.02; P=0.08).[31] The median survival among patients who received capecitabine plus gemcitabine was 7.1 months, versus 6.2 months among patients who received gemcitabine alone. The authors performed a meta-analysis of their study and two similar but smaller studies. These results showed a significant survival benefit with gemcitabine plus capecitabine as compared with gemcitabine alone (hazard ratio, 0.86; 95% CI, 0.75 to 0.98; P=0.02). The efficacy results obtained with gemcitabine in our study are in line with the results of these studies, as well as the findings in other trials of single-agent gemcitabine in patients with advanced pancreatic cancer.[4,29]

The patient-selection criteria in our study were more rigorous than those in previous studies. Patients had to have metastatic disease and a good performance status (ECOG status score of 0 or 1). Only 38% of our patients had carcinoma of the pancreatic head — a lower rate than in previous trials (52 to 70%).[6,31,32] This difference may be related to the exclusion of patients with a high bilirubin level, because of the increased risk of irinotecan-induced toxicity.[8] As a result of this exclusion criterion, the proportion of enrolled patients with biliary stents was low (14.3%). Cholangitis is a common complication of biliary stenting, and although it did not occur in any of the patients in our study, careful monitoring of the bilirubin level is required when irinotecan is administered in patients with biliary drainage.

The safety profile of FOLFIRINOX was less favorable than that of gemcitabine. FOLFIRINOX was associated with a higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia. Despite the higher incidence of adverse events associated with the FOLFIRINOX regimen, a significant increase in the time to definitive deterioration of the quality of life was observed in the FOLFIRINOX group as compared with the gemcitabine group.

In conclusion, our findings suggest that FOLFIRINOX is a first-line option for patients with metastatic pancreatic cancer who are younger than 76 years and who have a good performance status (ECOG 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels.

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(54) Title: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN

(57) Abstract: Provided are methods for treating pancreatic cancer in a patient by administering liposomal irinotecan (MM-398) alone or in combination with additional therapeutic agents. In one embodiment, the liposomal irinotecan (MM-398) is co-administered with 5-fluorouracil and leucovorin.

METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 61/659,211 (filed June 13, 2012) and U.S. Provisional Application No. 61/784,382 (filed March 14, 2013), both of which are incorporated herein by reference.

BACKGROUND

Despite improvements in cancer treatments, there remains a critical need to further improve therapies so as to prolong patients' lives while maintaining quality of life, particularly in the case of advanced cancers such as pancreatic cancers that often are, or become, resistant to current therapeutic modalities.

Incidence of pancreatic cancer has markedly increased during the past several decades. It now ranks as the fourth leading cause of cancer death in the United States. Pancreatic cancer's high mortality rate is due to a dearth of effective therapies and a complete absence of reliably durable therapies. Because of the location of the pancreas, pancreatic cancer is typically not diagnosed until a tumor has become large enough to produce systemic symptoms. This, coupled with the absence of good screening tools and a limited understanding of risk factors, results in patients usually having advanced disease, often advanced metastatic disease, at the time of diagnosis. Metastatic pancreatic cancer has a dismal prognosis and is almost uniformly fatal, with an overall survival rate of less than 4% at 5 years.

Chemotherapy with one or more of 5-fluorouracil (5-FU) and gemcitabine has been shown to prolong survival in pancreatic cancer. Combination therapies including folinic acid (leucovorin or levoleucovorin), 5-fluorouracil, and irinotecan (FOLFIRI), folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX), or, less commonly, a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) are also used to treat some pancreatic cancers. Irinotecan is 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycampothecin, IUPAC name (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. Irinotecan is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble

analog of the naturally-occurring alkaloid, camptothecin. Also known as CPT-11, irinotecan is currently marketed formulated as an aqueous solution as Camptosar® (irinotecan hydrochloride injection). Topoisomerase I inhibitors such as irinotecan work to arrest uncontrolled cell growth by inhibiting the unwinding of DNA and thereby preventing DNA replication.

The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug. Irinotecan is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38. SN-38 is not recognized by P-glycoprotein, a drug transporter that plays an important role in acquired drug resistance by pumping certain drugs out of cells, so irinotecan is likely to be active in tumors resistant to other standard chemotherapies. In the body, SN-38 is cleared via glucuronidation, for which major pharmacogenetic variability has been described, and biliary excretion. These drug properties contribute to the marked heterogeneities in efficacy and toxicity observed clinically with irinotecan. Irinotecan hydrochloride injection is approved in the United States for treatment of metastatic colon or renal cancer and is also used to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

There are few approved treatment options for advanced or metastatic pancreatic cancers, particularly for those of exocrine origin. Single-agent gemcitabine is the current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma. In clinical trials, single-agent gemcitabine has consistently demonstrated a median prolongation of survival of 5 to 6 months and a 1-year survival rate of about 20%. Single agent gemcitabine was also approved as second line treatment for patients previously treated with but no longer responsive to 5-fluorouracil, with a median overall prolongation of survival of 3.9 months.

Based upon what is known of the biology of pancreatic cancer, a variety of targeted agents have been evaluated, but only erlotinib, a protein tyrosine kinase inhibitor targeted to EGFR, has been approved for first-line use in advanced pancreatic cancer, and the approval is only for use in combination with gemcitabine. The co-administration of erlotinib with gemcitabine resulted in a statistically significant benefit in survival, and improvements in median survival (6.4 months vs. 5.9 months), and 1-year survival rate (24% vs. 17%) compared to gemcitabine alone. Clinical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative. Thus, there is an

urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer. The disclosed invention addresses this need and provides other benefits.

SUMMARY

Provided are methods for treating pancreatic cancer in a patient (*i.e.*, a human patient) comprising administering to the patient liposomal irinotecan (e.g., irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398) alone or in combination with 5-fluorouracil (5-FU) and leucovorin (together, 5-FU/LV), according to a particular clinical dosage regimen. Compositions adapted for use in such methods are also provided.

In one aspect, a method for treatment (*e.g.*, effective treatment) of pancreatic cancer in a patient is provided, the method comprising: administering to the patient, and affective amount of liposomal irinotecan, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2. In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

In another aspect, a method for treatment of pancreatic cancer in a patient is provided, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle of administration, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2, and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m^2 to 80 mg/m^2 (*e.g.*, 60 mg/m^2 or 70 mg/m^2 or 80 mg/m^2);

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form, or levoleucovorin) or 400 mg/m^2 (*l* + *d* racemic form).

In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2. In one embodiment, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes.

In another embodiment, the 5-FU is administered intravenously over 46 hours.

In another embodiment, leucovorin is administered intravenously over 30 minutes.

In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

In another embodiment, the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In one embodiment, treating the patient results in a positive outcome, wherein the positive outcome is pathologic complete response (pCR), complete response (CR), partial response (PR) or stable disease (SD). In another embodiment, the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy. In another embodiment, the liposomal irinotecan is formulated as irinotecan sucrose octasulfate salt liposome injection (MM-398). Irinotecan sucrose octasulfate salt liposome injection may also be referred to as irinotecan HCl liposome injection because irinotecan HCl is the active pharmaceutical ingredient that is used to load irinotecan into liposomes containing triethylammonium sucrose octasulfate to prepare MM-398 liposomes. This nomenclature may be used even though the hydrochloride ion of the irinotecan HCl reacts with the triethylammonium ion of the triethylammonium sucrose octasulfate to yield triethylammonium chloride (triethylamine hydrochloride), leaving irinotecan sucrose octasulfate salt as the entrapped pharmaceutical agent within the MM-398 liposomes. In another aspect, kits for treating pancreatic cancer in a patient are provided, the kit comprising a dose of liposomal irinotecan and instructions for using liposomal irinotecan as described herein.

In another aspect, kits for treating pancreatic cancer in a patient are provided, the kit comprising a dose of each liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, 5-FU, and leucovorin as described herein.

In one embodiment, the kit encompasses treating an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In one embodiment, the liposomal irinotecan is liposomal irinotecan sucrose octasulfate salt injection (MM-398).

In another aspect, a formulation of liposomal irinotecan for co-administration with 5-fluorouracil (5-FU) and leucovorin in at least one cycle is provided, wherein the cycle is a period of 2 weeks, the formulation of irinotecan is a liposomal formulation of irinotecan, and wherein:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form, or levoleucovorin) or 400 mg/m^2 (*l* + *d* racemic form).

In one embodiment, after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2. In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes.

In another embodiment, the 5-FU is administered intravenously over 46 hours.

In another embodiment, leucovorin is administered intravenously over 30 minutes.

In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

In another embodiment, the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma,

adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In another embodiment, the liposomal formulation of irinotecan is irinotecan sucrose octasulfate salt liposome injection.

In another aspect is provided a method of improving chemotherapy outcomes by increasing tumor vascularity, the method comprising administering to a patient having a tumor an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and concomitantly administering an effective amount of a chemotherapy agent other than irinotecan to the patient.

In another aspect is provided irinotecan sucrose octasulfate salt liposome injection for concomitant administration to a patient having a tumor of 1) an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and 2) an effective amount of a chemotherapy agent other than irinotecan.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the anti-tumor activity of MM-398 in an orthotopic pancreatic tumor model expressing luciferase (L3.6pl).

Figure 2 is a graph showing accumulation of SN-38 in tumors following treatment with free irinotecan or liposomal irinotecan (MM-398).

Figure 3 is a graph showing the effect of MM-398 on Carbonic Anhydrase IX Staining in a HT29 Xenograft Model.

Figure 4 shows the effect of MM-398 on perfusion of small molecule Hoechst stain.

Figure 5 summarizes the pharmacokinetics of MM-398 in q3w (irinotecan, liposome + free drug).

Figure 6 summarizes the pharmacokinetics of MM-398 in q3w.

Figure 7 is a schematic illustration of a Phase 3 study design.

DETAILED DESCRIPTION

I. Definitions

As used herein, the term "subject" or "patient" is a human cancer patient.

As used herein, "effective treatment" refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder. A

beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer. Effective treatment may refer to alleviation of at least one symptom of a cancer. Such effective treatment may, e.g., reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.

The term "effective amount" refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

The terms "combination therapy," "co-administration," "co-administered" or "concurrent administration" (or minor variations of these terms) include simultaneous administration of at least two therapeutic agents to a patient or their sequential administration within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

The term "monotherapy" refers to administering a single drug to treat a disease or disorder in the absence of co-administration of any other therapeutic agent that is being administered to treat the same disease or disorder.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (*e.g.*, per hour, per day, per week, per month, etc.) to a patient. Such parameters include, *e.g.*, the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, *e.g.*, taken at a single administration, *e.g.*, orally (*e.g.*, as one, two, three or more pills, capsules, etc.) or injected (*e.g.*, as a bolus). Dosage sizes may also relate to doses that are administered continuously (*e.g.*, as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

As used herein, "cancer" refers to a condition characterized by abnormal, unregulated, malignant cell growth. In one embodiment, the cancer is an exocrine pancreatic cancer. In another embodiment, the exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

The terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent.

II. Irinotecan sucrose sulfate liposome injection (MM-398; PEP02)

As provided herein, irinotecan is administered in a stable liposomal formulation as irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"), the formulation referred to herein as "MM-398" (also known as PEP02, see US 8,147,867). MM-398 may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of MM-398 may be diluted, *e.g.*, in 500mL of 5% dextrose injection USP and infused over a 90 minute period.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The

lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules.

This stable liposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process. The long circulating pharmacokinetics and high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR allows for deposition of the liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor.

Pharmacogenetics of Irinotecan Glucuronidation

The enzyme produced by the UGT1A1 gene, UDP-glucuronosyltransferase 1, is responsible for bilirubin metabolism and also mediates SN-38 glucuronidation, which is the initial step in the predominant metabolic clearance pathway of this active metabolite of irinotecan. Besides its anti-tumor activity, SN-38 is also responsible for the severe toxicity sometimes associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form, SN-38 glucuronide, is an important step in the modulation of irinotecan toxicity.

Mutational polymorphisms in the promoter of the UGT1A1 gene have been described in which there is a variable number of thymine adenine (ta) repeats. Promoters containing seven thymine adenine (ta) repeats (found in the UGT1A1*28 allele) have been found to be less active than the wild-type six repeats, resulting in reduced expression of UDP-glucuronosyltransferase 1. Patients who carry two

deficient alleles of UGT1A1 exhibit reduced glucuronidation of SN-38. Some case reports have suggested that individuals who are homozygous for UGT1A1*28 alleles (referred to as having the UGT1A1 7/7 genotype, because both alleles are UGT1A1*28 alleles that contain 7 ta repeats, as opposed to the wild-type UGT1A1 6/6 genotype in which both alleles contain 6 ta repeats) and who have fluctuating elevation in serum bilirubin, (*e.g.*, Gilbert's Syndrome patients), may be at greater risk of toxicity upon receiving standard doses of irinotecan. This suggests that there is a link between homozygosity of the UGT1A1*28 allele, bilirubin levels and irinotecan toxicity.

The metabolic transformation of MM-398 to SN-38 (*e.g.*, in plasma) includes two critical steps: (1) the release of irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. While not intending to be limited by theory, it is believed that once irinotecan leaves the liposomes, it is catabolized by the same metabolic pathways as conventional (free) irinotecan. Therefore the genetic polymorphisms in humans predictive for the toxicity and efficacy of irinotecan and those of MM-398 can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance, higher systemic exposure and longer elimination half-life of SN-38 of the MM-398 formulation compared to free irinotecan, the deficient genetic polymorphisms may show more association with severe adverse events and/or efficacy.

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) have been shown to be at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan (Camptosar®), in a study of 66 patients who received single-agent irinotecan (350 mg/m2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. Importantly, no grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of life threatening neutropenia is described. For this reason, patients who are enrolled in the phase 3 study described in the Examples herein and are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) will have MM-398 treatment initiated at

a lower dose than patients with one (*e.g.*, UGT1A1 6/7) or two (UGT1A1 6/6) wild-type alleles.

Additional genotypic modifiers of irinotecan metabolism

Although the UGT1A1*28 allele is relatively common in Caucasians (estimates 10%), the prevalence is varied in other ethnic groups. Furthermore, additional UGT1A1 genotypes are found with higher prevalence for example in Asian populations and these could be important for the metabolism of irinotecan in these populations. For example, the UGT1A1*6 allele is more prevalent in Asians. This allele is not associated with a ta repeat, but with a Gly71Arg mutation that reduces enzyme activity. In previous and ongoing studies of MM-398, pharmacogenetic information has been collected on patients being enrolled. In a study referred to as the PEP0203 study, the relationship of genetic polymorphism of UGT1A family and of DPYD (dihydropyrimidine dehydrogenase, an enzyme associated with catabolism of 5-FU) with pharmacokinetic parameters of MM-398 and toxicity did not provide a clear correlation with the small sample size of subjects evaluated. However, it was observed that patients with UGT1A1*6/*28 combined polymorphism had higher dose-normalized AUCs of SN-38 and experienced DLT.

III. 5-Fluorouracil (5-FU) and Leucovorin

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

Leucovorin (also called folinic acid) acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levoleucovorin") has

also been approved by the FDA for treatment of cancer. The dosage of levoleucovorin is typically half that of the racemic mixture containing both dextro (*d*) and levo (*l*) isomers.

FU and leucovorin will be stored and handled according to the country specific package inserts.

IV. Administration

Liposomal irinotecan is administered intravenously, either alone or in combination with 5-fluorouracil (5-FU) and/or leucovorin. In one embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin. In another embodiment, leucovorin is administered prior to 5-FU. In another embodiment, liposomal irinotecan is administered intravenously over 90 minutes. In another embodiment, 5-FU is administered intravenously over 46 hours. In another embodiment, leucovorin is administered intravenously over 30 minutes. In various embodiments the liposomal irinotecan is MM-398.

V. Patient Populations

In one embodiment, a patient treated using the methods and compositions disclosed herein exhibits evidence of recurrent or persistent pancreatic cancer following primary chemotherapy.

In another embodiment, the patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

In one embodiment a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

In another embodiment, the pancreatic cancer of the patient undergoing treatment is advanced pancreatic cancer, which is a pancreatic tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor.

The compositions and methods disclosed herein are useful for the treatment of all pancreatic cancers, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments.

VI. Combination Therapy

In one embodiment, liposomal irinotecan is co-administered to patients having pancreatic cancer in combination with 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen, such as those described herein. In one embodiment, the liposomal irinotecan is MM-398.

As used herein, adjunctive or combined administration (coadministration) includes simultaneous administration of the compounds in the same or different dosage form, or separate administration of the compounds (e.g., sequential administration). For example, liposomal irinotecan can be simultaneously administered with 5-FU and leucovorin. Alternatively, liposomal irinotecan can be administered in combination with 5-FU and leucovorin, wherein liposomal irinotecan, 5-FU and leucovorin are formulated for separate administration and are administered concurrently or sequentially. For example, liposomal irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the 5-FU and leucovorin. Such concurrent or sequential administration preferably results in liposomal irinotecan, 5-FU, and leucovorin being simultaneously present in treated patients. In a particular embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin. In another particular embodiment, leucovorin is administered prior to 5-FU.

In another embodiment, liposomal irinotecan, 5-FU, and leucovorin are formulated for intravenous administration. In a particular embodiment, the patient is administered an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a) liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2; (b) 5-FU is administered at a dose of 2400 mg/m^2; and (c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form) In a particular embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2.

In one embodiment, liposomal irinotecan may be initially administered at a high dose and may be lowered over time. In another embodiment, liposomal

irinotecan is initially administered at a low dose and increased over time. In one embodiment, liposomal irinotecan is administered as a monotherapy.

In another embodiment, the dose of 5-FU is varied over time. For example, 5-FU may be initially administered at a high dose and may be lowered over time. In another embodiment, 5-FU is initially administered at a low dose and increased over time.

In another embodiment, the dose of leucovorin is varied over time. For example, leucovorin may be initially administered at a high dose and may be lowered over time. In another embodiment, leucovorin is initially administered at a low dose and increased over time.

VII. Treatment Protocols

Suitable treatment protocols include, for example, those wherein the patient is administered an effective amount of liposomal irinotecan, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2. In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

In another embodiment, the treatment protocol includes administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a) liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2; (b) 5-FU is administered at a dose of 2400 mg/m^2; and (c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form). In a particular embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2.

VIII. Outcomes

Provided herein are methods for treating pancreatic cancer in a patient comprising administering to the patient liposomal irinotecan (MM-398), alone or in combination with 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen.

Preferably, the combination therapy with liposomal irinotecan with 5-FU and leucovorin exhibits therapeutic synergy.

"Therapeutic synergy" refers to a phenomenon where treatment of patients with a combination of therapeutic agents manifests a therapeutically superior outcome to the outcome achieved by each individual constituent of the combination used at its optimum dose (T. H. Corbett et al., 1982, Cancer Treatment Reports, 66, 1187). In this context a therapeutically superior outcome is one in which the patients either a) exhibit fewer incidences of adverse events while receiving a therapeutic benefit that is equal to or greater than that where individual constituents of the combination are each administered as monotherapy at the same dose as in the combination, or b) do not exhibit dose-limiting toxicities while receiving a therapeutic benefit that is greater than that of treatment with each individual constituent of the combination when each constituent is administered in at the same doses in the combination(s) as is administered as individual components. In xenograft models, a combination, used at its maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its individual maximum tolerated dose, manifests therapeutic synergy when decrease in tumor growth achieved by administration of the combination is greater than the value of the decrease in tumor growth of the best constituent when the constituent is administered alone.

Thus, in combination, the components of such combinations have an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to monotherapy with liposome-encapsulated irinotecan alone or treatment with the chemotherapeutic(s) in the absence of liposomal irinotecan therapy. By "additive" is meant a result that is greater in extent (e.g., in the degree of reduction of tumor mitotic index or of tumor growth or in the degree of tumor shrinkage or the frequency and/or duration of symptom-free or symptom-reduced periods) than the best separate result achieved by monotherapy with each individual component, while "superadditive" is used to indicate a result that exceeds in extent the sum of such separate results. In one embodiment, the additive effect is measured as slowing or

stopping of pancreatic tumor growth. The additive effect can also be measured as, e.g., reduction in size of a pancreatic tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, increase in overall response rate, or increase in median or overall survival.

One non-limiting example of a measure by which effectiveness of a therapeutic treatment can be quantified is by calculating the log10 cell kill, which is determined according to the following equation:

log10 cell kill = T C (days)/3.32 × Td

in which T C represents the delay in growth of the cells, which is the average time, in days, for the tumors of the treated group (T) and the tumors of the control group (C) to have reached a predetermined value (1 g, or 10 mL, for example), and Td represents the time, in days necessary for the volume of the tumor to double in the control animals. When applying this measure, a product is considered to be active if log10 cell kill is greater than or equal to 0.7 and a product is considered to be very active if log10 cell kill is greater than 2.8. Using this measure, a combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose generally less than or equal to its maximum tolerated dose, exhibits therapeutic synergy when the log10 cell kill is greater than the value of the log10 cell kill of the best constituent when it is administered alone. In an exemplary case, the log10 cell kill of the combination exceeds the value of the log10 cell kill of the best constituent of the combination by at least 0.1 log cell kill, at least 0.5 log cell kill, or at least 1.0 log cell kill.

Responses to therapy may include:

Pathologic complete response (pCR): absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

Partial Response (PR): At least a 30% decrease in the sum of dimensions of target lesions, taking as reference the baseline sum diameters;

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) denotes at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression.

In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of pancreatic cancer.

In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as $\geq$10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target lesions, e.g., pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response

or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In some embodiments, administration of effective amounts of liposomal irinotecan, 5-FU and leucovorin according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a breast tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate (CBR = CR+ PR+ SD $\geq$ 6 months) better than that achieved by the same combinations of anti-cancer agents administered without concomitant MM-398 administration. In other embodiments, the improvement of clinical benefit rate is about 20% 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to the same combinations of anti-cancer agents administered without concomitant MM-398 administration.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1: Activity of MM-398 in an Orthotopic Pancreas Tumor Model Expressing Luciferase (L3.6pl)

The anti-tumor activity of MM-398 was assessed in an orthotopic pancreatic cancer model (L3.6pl), a highly hypoxic preclinical tumor model. Approximately 2.5 x 10^{-5} L3.6pl pancreatic tumor cells were implanted by direct injection into the pancreas. The bioluminescence images (BLI) were followed over time for tumor burden detection/quantitation. MM-398 and free irinotecan were dosed at a dose of 20 mg/kg/dose weekly for three weeks. As shown in Figure 1, MM-398 (liposomal CPT11) had significant anti-tumor activity, as compared to a control (HBS) and free CPT11.

Example 2: Accumulation of SN-38 in Tumors Following Treatment with Free Irinotecan or Liposomal Irinotecan (MM-398)

It was hypothesized that the anti-tumor activity observed in the orthotopic pancreatic cancer model is due to the effect of macrophages in converting irinotecan

to the more active SN-38 locally. To test this hypothesis, human colon cancer cells (HT-29) were injected subcutaneously into SCID mice, 40 mg/kg of free irinotecan or MM-398 was injected intravenously when the tumors reached 1000 mm^3 in size. Tumor-bearing mice were sacrificed at different time points, tumors from both groups were extracted and the concentrations of SN-38 were measured.

As shown in Figure 2, there was a 20-fold increase in the tumor AUC_{SN-38} for MM-398 as compared to free irinotecan. The long duration of exposure allows for prolonged exposure of the slow proliferating cancer cells to the active metabolite as they progress through the cell cycle. In addition, this activity was also hypothesized to result from a reduction in intra-tumoral hypoxia, and the subsequent downstream effects on angiogenesis, metastasis, and the immunosuppressive environment in tumors.

Example 3: Effect of MM-398 on Carbonic Anhydrase IX Staining in a HT29 Xenograft Model

To test whether MM-398 reduces markers of hypoxia, experiments were conducted in a human colon cancer cell (HT-29) model. Specifically, HT-29 cells were injected subcutaneously into nude mice, on day 13 either PBS control or 1.25, 2.5, 5, 10 or 20 mg/kg MM-398 was injected intravenously. MM-398 was dosed once a week for 4 weeks at the indicated doses. Tumors from both groups (n = 5) were extracted 24 hours after the last dose. Frozen tumor sections were used for immunohistochemical staining of Carbonic Anhydrase IX (CAIX). Quantification of CAIX staining was performed using Definiens® (Definiens AG, Munich) software.

As shown in Figure 3, MM-398 reduced markers of hypoxia. Specifically, the graphs in Figure 3 show the percentage of cells that stained with medium (middle third) or high (top third) intensity for CAIX. Representative samples from each group are shown as well as the group average (mean +/- stdev). MM-398 treatment modifies the tumor microenvironment by decreasing the percentage of both medium and high CAIX positive cells in a dose-dependent manner. As hypoxia is a hallmark of resistant and aggressive disease, a reduction in hypoxia is expected to make tumor cells more sensitive to chemotherapies.

Example 4: MM-398 Increases Perfusion of Hoechst Stain

In addition to changing the chemosensitivity of tumor cells through modification of the tumor microenvironment, lowering hypoxia can indicate improved tumor vascularization, which can facilitate delivery of small molecule therapies.

MM-398 treatment led to increased microvessel density 6 days after treatment as measured by CD31 (platelet endothelial cell adhesion molecule) staining in an HT29 xenograft study. To further assess the effect of MM-398 on small molecule tumor vascularization, a Hoechst 33342 perfusion experiment was conducted. Specifically, a primary pancreatic tumor was grown in NOD-SCID mice and given one dose of MM-398 (20mg/kg). After 24 hours, Hoechst 33342 stain was administered 20 minutes prior to sacrificing the animal. As shown in Figure 4, the increase in stain intensity in treated mice was statistically significant, $p < 0.001$. These data indicate that MM-398 modifies the tumor microenvironment in a manner that should make tumors more susceptible to agents such as 5-FU/LV, through decreasing tumor hypoxia and increasing small molecule perfusion.

Example 5: MM-398 Pharmacokinetics in Humans (Phase I)

The pharmacokinetic profile of MM-398 single agent was investigated in a phase I clinical study (PEP0201) in patients at 60, 120 or 180mg/m^2 dose levels and in a phase II clinical trial in gastric cancer patients (PEP0206) at 120mg/m^2. Plasma levels of total irinotecan, SN-38 and encapsulated irinotecan were measured in these studies.

The peak serum concentrations of total irinotecan (C_{max}) ranged from 48-79 μg/ml for 120mg/m^2 of MM-398, which was approximately 50 fold higher than 125mg/m^2 free irinotecan. The total irinotecan half-life ($t_{1/2}$) for MM-398 ranged from 21 to 48 hours, which was approximately 2-3 fold higher than 125mg/m^2 of free irinotecan. Overall, total irinotecan exposure at one week (AUC 0–T) ranged from 1200- 3000 (μg*h/ml) at a dose of 120 mg/m^2 of MM-398, approximately 50-100 fold higher than 300mg/m^2 of free irinotecan. In contrast, SN38 C_{max} levels at 120mg/m^2 of MM-398 ranged from 9 to 17 ng/ml, which was approximately 50% less than free irinotecan at 125mg/m^2. Overall, exposure of SN38 at one week (AUC 0-T) ranged from 474 to 997 ng*/ml and was only 1-2 fold higher than achieved by free irinotecan at 300mg/m^2. For both SN38 and total irinotecan, AUC increased less than proportionally with dose of MM-398. The PK parameters of encapsulated irinotecan almost matched that of total irinotecan indicates that most of irinotecan remained encapsulated in the liposomes during circulation. The MM-398 PK parameters were not significantly changed when combined with 5-FU/LV. Figures 5 and 6 summarize the PK findings in previous studies of MM 398.

Example 6: Phase 1 Dose Escalation Study

A regimen combining fluorouracil, leucovorin, and MM-398 was studied in a phase 1 trial of solid tumors in 16 subjects, of whom 5 were patients with pancreatic cancer. The objective tumor response rate, duration of response, and disease control rate were efficacy endpoints of the study. Among the 15 efficacy-evaluable patients, 2 (13.3%) had confirmed PR, 9 (60.0%) had SD, and 4 (26.7%) had PD. The overall disease control rate was 73.3%. Partial response was observed in one gastric cancer patient (at 80mg/m^2 dose level) and one breast cancer patient (at 100 mg/m2 dose level), with the duration of response of 142 and 76 days, respectively. Among the 6 patients who received the MTD dose of 80 mg/m^2, there were 1 PR, 4 SD and 1 PD. The tumor response rate and disease control rate were 16.7% and 83.3%, respectively. The main DLTs were grade 3 diarrhea, leucopenia, neutropenia and febrile neutropenia. The MTD for MM-398 was 80mg/m^2.

In the phase 1 dose-escalation study of MM-398 in combination with 5-FU/LV in advanced solid tumors (PEP0203), a total of 401 episodes of AE were reported from the 16 treated subjects (safety population), of which 74 (18.4%) were of CTC grade 3 or above. Among all AEs, 231 (57.6%) were considered by the investigators to be treatment-related. The most common treatment-related AEs, included nausea (81.3%), diarrhea (75.0%), vomiting (68.8%), fatigue (43.8%), mucositis (43.8%), leucopenia (37.5%), neutropenia (37.5%), weight loss (37.5%), anemia (31.3%), and alopecia (31.3%). Acute cholinergic diarrhea was rarely observed. Table 1 provides the incidence of treatment-emergent adverse events by maximum CTC grade and by causality (incidence ≥ 20%), as seen in the PEP0203 study. Table 2 provides the incidence of grade 3 or higher treatment-emergent adverse events seen in the 5 pancreatic cancer patients treated in the PEP0203 study.

Table 1: Incidence of treatment-emergent adverse events by maximum CTC grade and

by causality (incidence ≥ 20%) in the PEP0203 Study

System organ class Preferred Term	Total (N = 16)	Severity (Grade)[1]				Causality[2]	
		I	II	III	IV	Yes	No
Blood and lymphatic system disorders							
Anemia	7 (43.8%)	3	2	2	0	5	2
Leucopenia	6 (37.5%)	0	3	2	1	6	0

System organ class Preferred Term	Total (N = 16)	Severity (Grade)[1]				Causality[2]	
		I	II	III	IV	Yes	No
Neutropenia	6 (37.5%)	0	2	3	1	6	0
Gastrointestinal disorders							
Abdominal pain	7 (43.8%)	3	2	2	0	3	4
Constipation	6 (37.5%)	3	3	0	0	0	6
Diarrhea	12 (75.0%)	3	4	5	0	12	0
Nausea	13 (81.3%)	6	6	1	0	13	0
Vomiting	12 (75.0%)	3	8	1	0	11	1
General disorders and administration site conditions							
Fatigue	8 (50.0%)	4	3	1	0	7	1
Mucosal inflammation	7 (43.8%)	4	3	0	0	7	0
Pyrexia	7 (43.8%)	3	4	0	0	2	5
Infections and infestations							
Infection	6 (37.5%)	0	3	3	0	2	4
Investigations							
ALT increased	5 (31.3%)	3	2	0	0	4	1
AST increased	4 (25.0%)	3	1	0	0	1	3
Weight decreased	8 (50.0%)	4	4	0	0	6	2
Metabolism and nutrition disorders							
Anorexia	4 (25.0%)	1	2	1	0	3	1
Hypoalbuminaemia	4 (25.0%)	0	3	1	0	0	4
Hypocalcaemia	5 (31.3%)	1	4	0	0	0	5
Hypokalaemia	8 (50.0%)	2	0	5	1	2	6
Hyponatraemia	4 (25.0%)	2	0	0	2	0	4
Nervous system disorders							
Dizziness	4 (25.0%)	4	0	0	0	1	3
Psychiatric disorders							
Insomnia	4 (25.0%)	4	0	0	0	1	3
Respiratory, thoracic and mediastinal disorders							
Cough	5 (31.3%)	3	1	1	0	0	5
Skin and subcutaneous tissue disorders							
Alopecia	5 (31.3%)	5	0	0	0	5	0

[1]: Severity grading used the highest grading ever rated for each subject if the subject had such adverse event reported

[2]: Defined as subject ever experienced AE related to the study drug in causality or not

Table 2: Incidence of Grade 3 or higher treatment-emergent adverse events in pancreatic cancer patients in the PEP0203 Study

	Overall N=5	60 mg/m2 N=1	80 mg/m2 N=3	120 mg/m2 N=1
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)
-Any primary system organ class				
-Total	3 (60.0)	0	2 (66.7)	1 (100.0)
Infections and infestations				
-Total	3 (60.0)	0	2 (66.7)	1 (100.0)
Hepatitis viral	1 (20.0)	0	1 (33.3)	0
Infection	1 (20.0)	0	0	1 (100.0)
Pneumonia	1 (20.0)	0	1 (33.3)	0
Septic shock	1 (20.0)	0	1 (33.3)	0
Blood and lymphatic system disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Lymphopenia	1 (20.0)	0	0	1 (100.0)
Neutropenia	1 (20.0)	0	1 (33.3)	0
White blood cell disorder	1 (20.0)	0	0	1 (100.0)
Gastrointestinal disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Diarrhoea	2 (40.0)	0	1 (33.3)	1 (100.0)
Abdominal pain	1 (20.0)	0	0	1 (100.0)
Gastrointestinal haemorrhage	1 (20.0)	0	1 (33.3)	0
Investigations				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Blood bilirubin increased	1 (20.0)	0	1 (33.3)	0
Lipase increased	1 (20.0)	0	0	1 (100.0)
Neutrophil count decreased	1 (20.0)	0	0	1 (100.0)
White blood cell count decreased	1 (20.0)	0	0	1 (100.0)
Metabolism and nutrition disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Hypoalbuminaemia	1 (20.0)	0	1 (33.3)	0
Hypokalaemia	1 (20.0)	0	1 (33.3)	0
Hyponatraemia	1 (20.0)	0	0	1 (100.0)
Hypophosphataemia	1 (20.0)	0	0	1 (100.0)

Primary system organ class Preferred term	Overall N=5 n (%)	60 mg/m2 N=1 n (%)	80 mg/m2 N=3 n (%)	120 mg/m2 N=1 n (%)
Respiratory, thoracic and mediastinal disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Dyspnoea	1 (20.0)	0	0	1 (100.0)
Pleural effusion	1 (20.0)	0	1 (33.3)	0
General disorders and administration site conditions				
-Total	1 (20.0)	0	0	1 (100.0)
Death	1 (20.0)	0	0	1 (100.0)

Example 7: Phase 3 Trial

The promising efficacy and safety data from the Phase 1 Trial (described above) warrant the MM-398 and 5-FU plus leucovorin combination to be explored further in a phase 3 study.

A. Objectives

The primary objective of the Phase 3 trial is to compare overall survival following treatment with MM-398, with or without 5-fluorouracil plus leucovorin, versus 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer that have progressed on gemcitabine based therapy. The secondary objectives includes the following:

To compare time-to-event efficacy endpoints between the experimental and control arms (i.e., Progression-free survival (PFS) and Time to treatment failure (TTF));

- To compare the Objective Response Rate (ORR) between the treatment arms;
- To compare the tumor marker response of CA 19-9 between the treatment arms;
- To compare the Clinical Benefit Response (CBR) rate between the treatment arms;

- To assess patient-reported outcomes (PROs) between the treatment arms using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30);
- To compare the safety and adverse event profile between the treatment arms; and
- To determine the pharmacokinetic properties of MM-398, as a single agent and in combination with 5-FU and leucovorin.

A key exploratory objective of this study is to explore biomarkers associated with toxicity and efficacy following treatment with MM-398 and MM-398 plus 5-FU and leucovorin.

B. Study Design

This is an open label, randomized, three arm, Phase 3 trial of MM-398, with or without 5-FU and leucovorin, versus 5-fluorouracil (5-FU) and leucovorin (also known as folinic acid), in metastatic pancreatic cancer patients who have progressed on prior gemcitabine based therapy.

Approximately 405 eligible patients will be enrolled in this global study, under the protocol version 2 or later. All patients will participate in up to 28 days of screening, during which they will be assessed for eligibility and screened for the UGT1A1*28 allele. Eligible patients will be randomized, in a 1:1:1 ratio, to one of the following treatment arms:

Arm A (experimental arm): MM-398	MM 398 120 mg/m2 IV over 90 minutes, every 3 weeks. Patients who are homozygous for UGT1A1*28 allele will receive the first cycle of therapy at a reduced dose of 80 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased in increments of 20 mg/m^2 up to a maximum of 120 mg/m^2.
Arm B (control arm): 5-FU and leucovorin	**5-FU 2000 mg/m^2 IV over 24-hours (+/- 30 minutes), administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle.** **Levoleucovorin dosed at 200 mg/m^2 or the leucovorin *l* + *d* racemic mixture dosed at 400 mg/m^2, given IV over 30 minutes, administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle.**
Arm C (experimental arm): MM-398, 5-FU and	**MM-398 80 mg/m^2 IV over 90 minutes, every 2 weeks. Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of**

leucovorin	**therapy at a reduced dose of 60 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m^2.** **5-FU 2400 mg/m^2 IV over 46-hours, every 2 weeks.** **Levoleucovorin dosed at 200 mg/m^2 or the l + d racemic mixture dosed at 400 mg/m^2, IV over 30 minutes, every 2 weeks.** **MM-398 should be administered prior to 5-FU and leucovorin; leucovorin should always be administered prior to 5-FU. If the dosing of either MM-398 or 5-FU/leucovorin needs to be withheld, then the other drug in the combination should not be administered either.**

Patients will be evenly randomized to the treatment arms using an Interactive Web Response System (IWRS) at a central location. The randomization will be stratified based on the following prognostic factors:

- Baseline albumin levels ($\geq$ 4.0 g/dL *vs* < 4.0 g/dL)
- KPS (70 and 80 *vs* $\geq$ 90)
- Ethnicity (Caucasian *vs* East Asian *vs* All Others)

Therapy will be administered in cycles. Patients will be treated until disease progression (radiologic or clinical deterioration), intolerable toxicity or other reasons for study termination. Tumor responses will be assessed, using the RECIST guidelines (Eisenhauer, E.A., *et al.*, "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, 2009. 45:pp. 228-247) every 6 weeks or sooner if disease progression based on clinical signs and symptoms is evident. Tumor measurement images will be collected and stored on all patients throughout the study. However, all treatment decisions will be based on the local radiologist and/or PI assessment of disease status. An independent review of the scans may be performed in the event that an independent analysis of ORR and/or PFS is necessary.

Following treatment discontinuation a 30-day post therapy follow up visit is required. Subsequently, all patients will be followed-up every 1 month for overall survival (by phone or visit to the study site) until death or study closure, whichever occurs first. Patients, who withdraw from study treatment due to reasons other than objective disease progression, should continue to be assessed every 6 weeks during the follow-up period for radiologic progression (including patients who discontinue due to symptomatic deterioration).

All patients will be asked to complete a pain assessment and analgesic consumption diary throughout their participation in the study, which will document the patient's assessment of their pain intensity and daily analgesic consumption. Patient responses will be used for assessment of the clinical benefit response along with the other parameters. All patients will also be required to complete the EORTC-QLQ-C30 questionnaire for assessing quality of life.

In order to address the exploratory objectives of this study, all sites will be required to participate in the companion translational research (TR) protocol (MM-398-07-03-01.TR), unless prohibited by local regulations. Participation is this study will be optional for patients and they will be required to provide a separate consent for the translational research.

The primary analysis of OS will take place once at least 305 deaths events have occurred in patients enrolled under protocol version 2 or later. Patients receiving study treatment at the time of primary analysis for OS will continue to receive treatment until one of the criteria for discontinuation is met. During the course of the study, regular review of safety data will be conducted by an independent data safety monitoring board (DSMB). Figure 7 illustrates the study design.

C. Patient Selection and Discontinuation

Approximately 405 patients will be enrolled globally in this study, under the protocol version 2 or later. In order to be included in the study, patients must have/be:

1. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
2. Documented metastatic disease; disease status may be measurable or non-measurable as defined by RECIST v1.1 guidelines
3. Documented disease progression after prior gemcitabine or gemcitabine containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies include, but are not limited to:
    - Single agent gemcitabine
    - Any one gemcitabine-based regimen, with or without maintenance gemcitabine
    - Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added

- Gemcitabine administered in the adjuvant setting if disease recurrence occurred within 6 months of completing the adjuvant therapy

4. Karnofsky Performance Status (KPS) ≥ 70
5. Adequate bone marrow reserves as evidenced by:
    - ANC > 1,500 cells/μl without the use of hematopoietic growth factors; and
    - Platelet count > 100,000 cells/μl; and
    - Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL)
6. Adequate hepatic function as evidenced by:
    - Serum total bilirubin within normal range for the institution (biliary drainage is allowed for biliary obstruction)
    - Albumin levels ≥ 3.0 g/dL
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present)
7. Adequate renal function as evidenced by a serum creatinine ≤ 1.5 x ULN
8. Normal ECG or ECG without any clinically significant findings
9. Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy
10. At least 18 years of age
11. Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

1. Active CNS metastases (indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease)
2. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1
3. History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible.

Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years.

4. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
5. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
6. Active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome
7. Known hypersensitivity to any of the components of MM-398, other liposomal products, fluropyrimidines or leucovorin
8. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study
9. Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results
10. Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a reliable method of birth control, during the study and for 3 months following the last dose of study drug.

The criteria for enrollment must be followed explicitly. Patients will be discontinued from the study treatment in the following circumstances:

- Patient has evidence of disease progression based on RECIST v1.1 criteria
- Patient shows symptomatic deterioration
- Patient experiences intolerable toxicity, or an adverse event which requires:
    - A third dose reduction

- Treatment to be withheld for more than 21 days from the start of next cycle, unless, in the opinion of the investigator, the patient is receiving benefit from study treatment

- Patient is significantly non-compliant with study procedures per PI assessment
- The patient or patient's attending physician requests that the patient be withdrawn from the study treatment
- The investigator or Sponsor, for any reason, but considering the rights, safety and well-being of the patient(s) and in accordance with ICH/GCP Guidelines and local regulations, stops the study or stops the patient's participation in the study

If a patient is lost to follow-up or withdraws from study treatment, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before considering the patient lost to follow-up. If a patient discontinues study treatment due to reasons other than objective disease progression, the patient should continue to have radiological disease assessment every 6 weeks until objective disease progression is observed.

All patients who discontinue study treatment should continue to be followed-up as required by the protocol. The only circumstance under which a patient should not be followed for study endpoints is when the patient has withdrawn consent. Withdrawal of consent should be a patient initiated decision and should mean, not only that the patient wishes to discontinue study treatment and follow-up visits but also that the investigator is no longer authorized to make further efforts to contact the patient, including any efforts to identify their survival status.

D. Method of Assigning Patients to Treatment Groups

After all screening assessments have been completed and UGT1A1*28 results are available, patients will be randomized using a computerized interactive web response system (IWRS), in a 1:1:1 ratio, to one of the following treatment arms:

- **Arm A** (experimental arm): MM-398
- **Arm B** (control arm): 5-FU and leucovorin
- **Arm C** (experimental arm): MM-398, 5-FU and leucovorin

Randomization must occur within 7 days of planned dosing. The randomization will be stratified based on the following prognostic factors:

- Baseline albumin levels (≥ 4.0 g/dL *vs* < 4.0g/dL)
- KPS (70 and 80 *vs* ≥ 90)
- Ethnicity (Caucasian *vs* East Asian *vs* All Others)

E. Description of MM-398

MM-398 is irinotecan (also known as CPT-11) encapsulated in a liposomal drug delivery system. It will be supplied as sterile, single-use vials containing 9.5 mL of MM-398 at a concentration of 5 mg/mL. The vials contain a 0.5 mL excess to facilitate the withdrawal of the label amount from each 10 mL vial.

MM-398 must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. MM-398 must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe.

MM-398 must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 6 hours if kept at room temperature (15-30°C).

Twenty vials of MM-398 will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

MM-398 will be dosed and administered as follows. All patients will be screened for UGT1A1*28 allele at baseline.

Arm A	• Patients who do not have the homozygous allele for UGT1A1*28 will receive MM-398 at a dose of 120 mg/m^2. • Any patient who is homozygous for UGT1A1*28 will receive the first cycle of therapy at a reduced dose of 80 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, their dose can be increased in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.
Arm C	• Patients who do not have the homozygous allele for UGT1A1*28 will receive MM-398 at a dose of 80 mg/m^2.

	• Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m^2. • MM-398 should be administered prior to 5-FU and leucovorin administration.

In Arm A, MM-398 will be administered by IV infusion over 90 minutes on the first day of each 3 week cycle, at the investigational site. In Arm C, MM-398 will be administered by an IV infusion over 90 minutes for the first cycle; the infusion time could be reduced to 60 minutes from cycle 2 onwards, if no acute infusion reaction has occurred in cycle 1. Cycle duration is 3 weeks for Arm A and 2 weeks for Arm C. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 3 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) to a final volume of 500mL. Care should be taken not to use in-line filters or any diluents other than D5W. MM-398 can be administered using standard PVC-containing intravenous administration bags and tubing.

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

All patients must be premedicated prior to MM-398 infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics as per standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

F. Description of 5-FU and Leucovorin

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

FU and leucovorin will be stored and handled according to the country specific package inserts. Commercially available 5-FU and leucovorin will be provided to all patients in the study who are randomized to Arm B and Arm C.

5-FU and leucovorin will be dosed and administered as follows.

Arm B	• 5-FU will be administered at a dose of 2000 mg/m^2 as an IV infusion over 24-hours, (+/- 30 minutes), every week for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 week cycle • Leucovorin will be administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + d racemic form) as an IV infusion over 30 minutes, every week for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 week cycle
Arm C	• 5-FU will be administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours, (+/- 60 minutes), every 2 weeks • Leucovorin will be administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + d racemic form) as an IV infusion over 30 minutes, every 2 weeks

Leucovorin should be reconstituted per the instructions on the package inset or standard institutional guidelines for reconstitution of leucovorin. Leucovorin should be administered prior to the 5-FU infusion.

Actual dose of 5-FU and leucovorin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

After cycle 1, for the start of each new cycle, a window period of +/- 3 days will be permitted, and a window period of +/- 1 day will be permitted for the Day 8, 15 and 22 infusions.

All patients must be premedicated prior to 5-FU and leucovorin infusion with standard doses of dexamethasone, prochlorperazine or equivalent other anti-emetics as per standard institutional practices for 5-FU administration.

G. Important Treatment Considerations with MM-398

Data from previous MM-398 studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the treatment procedures for managing those toxicities are provided below.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of MM-398, prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide. Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia, with discretion. Patients, who are known to have experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

Care of Intravenous Site

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended.

Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal

glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

Other Toxicity Potential

MM-398, the new liposome formulation of irinotecan, is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

H. Dose Modification Requirements

Dosing may be held for up to 3 weeks from when it was due, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Grade 1: Transient flushing or rash, drug fever <38° C (<100.4° F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1 • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2 • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 25-50 mg IV
Grade 3 • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary • No further treatment with MM-398 will be permitted
Grade 4 • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

I. MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm^3 (Worst CTCAE grade)	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28[d] Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28[d]
≥ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose
< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2[b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence[c, d]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study
[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

Table: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28[d] Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28[d]
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2[b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence[e, d]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m2 must be withdrawn from the study
[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

J. MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below. Infusion reactions should be handled as described above.

Table: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28[d] Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28[d]**
Grade 1 or 2 (2-3 stools/day > pretreatment or 4-6 stools/day > pretreatment)	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [e, d]

[a] All dose modifications should be based on the worst preceding toxicity

[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study

[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study

[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28

[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

Table: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia[d]

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28[e] Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28[e]**
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence [c, e]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [f, e]
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Optimize anti-emetic therapy **AND** reduce dose to 60 mg/m^2; if the patient is already receiving 60 mg/m^2, reduce dose to 50 mg/m^2 [c, e]	Optimize anti-emetic therapy **AND** reduce dose to 50 mg/m^2; if the patient is already receiving 50 mg/m^2, reduce dose to 40 mg/m^2 [f, e]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study
[d] Asthenia and Grade 3 Anorexia do not require dose modification
[e] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[f] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

K. 5-FU and Leucovorin Dose Modifications (Arm B and Arm C)

Guidelines for 5-FU dose modifications are provided below. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for MM-398 infusion reaction management should be used.

L. 5-FU Dose Modifications for Hematological Toxicities

Prior to the next dose in a cycle or prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq 1500/mm^3$
- WBC $\geq 3500/mm^3$
- Platelet count $\geq 75,000/mm^3$ (according to the European summary of product characteristics for 5-FU, the platelets should have recovered to $\geq 100,000/mm^3$ prior to initiating therapy)

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines provided in the table below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC ($cells/mm^3$)		Platelets ($cells/mm^3$)	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study

M. 5-FU Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until all Grade 3 or 4 non-hematological toxicities resolve to Grade 1 or baseline. Guidelines for dose adjustment of 5-FU related toxicities are provided below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[c] (Arm B & C)

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25% [b]	Reduce dose by 25% [b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25% [b], except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25%[b],except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study
[c] Asthenia and Grade 3 Anorexia do not require dose modification

N. Other Toxicities Requiring Special Attention

For both 5-FU and MM-398 treatment arms, QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated by with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhea as described above.

O. Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

Antiemetic Medications

Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered to all patients as premedications unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.

Colony Stimulating Factors

Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever; prophylactic use of G-CSF will be permitted only in those patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy or have had documented grade 3 or 4 neutropenia or neutropenic fever while receiving prior anti-neoplastic therapy.

Therapy for Diarrhea

Acute diarrhea and abdominal cramps, developing during or within 24 hours after MM-398 administration, may occur as part of a cholinergic syndrome. The syndrome will be treated with atropine. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms during the study.

Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea are abstracted below.

Table: Recommendations for Management of Chemotherapy Induced Diarrhea

Clinical Presentation	**Intervention**
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

The synthetic octapeptide octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 micrograms twice daily to 500 micrograms three times daily, with a maximum tolerated dose of 2000 micrograms three times daily in a 5-day regimen. Patients should be advised to drink water copiously throughout treatment.

Other Treatments

Symptomatic treatment for other toxicities should be per institutional guidelines. Prevention of alopecia with cold cap or of stomatitis with iced mouth rinses is allowed.

P. Prohibited Therapy

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any other that interact with irinotecan, should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the country specific package inserts of 5-FU and leucovorin for any other drug interactions.

The following therapies are not permitted during the trial:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy; palliative radiotherapy is permitted; and
- Any other investigational therapy is not permitted.

Q. Laboratory Procedures

Complete Blood Count

A complete blood count (CBC) will be performed locally, and must include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

Serum Chemistry

Serum chemistry panel will be performed centrally. Additionally, chemistry may also be assessed locally, and local lab results may be used for enrollment and

treatment decisions, if central lab results are not available. If local lab results are used for enrollment, then local lab results must be used for all subsequent treatment decisions. Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

CA 19-9

CA 19-9 levels will be measured centrally for all patients.

Pregnancy Test

All women of child bearing potential must undergo a urine or serum pregnancy test.

UGT1A1*28 Allele

A whole blood sample will be collected from all patients at baseline and sent to the central lab to test for UGT1A1*28 allele status. Local lab results may be used if the central lab results are not available at the time of randomization.

Pharmacokinetic Assessments

PK analysis will be done centrally. Plasma PK samples will be collected in Cycle 1, from all patients randomized in this study, at the following timepoints:

- Arm A: just prior to infusion, during infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of infusion and on C1D8
- Arm B: one sample at the end of 5-FU infusion (C1D2)
- Arm C: just prior to MM-398 infusion, during MM-398 infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of MM-398 infusion, at the end of 5-FU infusion and on C1D8

In addition, a PK sample will be collected in Cycle 1, any time between 8 and 72 hours following administration of MM-398, from patients randomized to Arm A and Arm C, who provide an additional consent for collection of this sample.

R. Pain Assessment and Analgesic Consumption

Pain assessment and analgesic consumption diaries will be provided to the patients for recording their pain intensity daily on a visual analogue scale and to document their daily analgesic use.

S. EORTC-QLQ-C30

Quality of life will be assessed by the EORTC-QLQ-C30 instrument. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included.

Patients will be required to complete the EORTC-QLQ-C30 questionnaire at timepoints outlined in the Schedule of Assessment. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients, for whom validated translations of the EORTC-QLQ-C30 questionnaire are available, will be required to complete the questionnaire.

T. Overall Survival/Post Study Follow-up

Overall survival data will be collected after a patient completes the 30 day follow-up visit, every 1 month (+/- 1 week) from the date of the 30 day follow-up visit. Post-discontinuation data to be collected will include: the date of disease progression (if not already documented; if patient discontinued from study treatment for reasons other than objective disease progression, patient should continue to undergo tumor assessment every 6 weeks, until commencement of new anti-neoplastic therapy or progressive disease); documentation of any anticancer treatment patient has received including the dates of any post-discontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. All patients must be followed-up until death or study closure, whichever occurs first.

U. Determining the Severity and Relatedness of Adverse Events

Each adverse event will be graded according to the NCI CTCAE V 4.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal, which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;

- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event
- **Fatal**: an event that results in the death of the patient

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

V. Analysis of the Overall Survival

Overall survival (OS) is the primary endpoint of this study. Overall survival is defined as the time from the date of patient randomization to date of death or the date last known alive. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data cut-off date.

The study primary analysis will involve two pair-wise comparisons of survival between the study treatments, in the ITT population using un-stratified Log Rank Test. The testing will be according to the Bonferroni-Holm procedure which strongly controls the family-wise error rate at 0.05 (two-sided) level [25]:

Reject $H_D^1: S_A(t) = S_B(t)$, i.e. no effect of MM-398 monotherapy relative to control, if the logrank p-value for this test is less than 0.025 or if the logrank p-value for this test is less than 0.05 and the logrank p-value for the comparison between Arm B and Arm C is less than 0.025.

Reject $H_D^2: S_C(t) = S_B(t)$, i.e. no effect of MM-398 combination therapy relative to control, if the logrank p-value for this test is less than 0.025 or if the logrank p-value for this test is less than 0.05 and the logrank p-value for the comparison between Arm A and Arm B is less than 0.025.

Kaplan-Meier analyses will be performed on each treatment group to obtain nonparametric estimates of the survival function and the median survival time. Corresponding 95% confidence intervals will be computed using the log-log method.

Cox proportional hazards modeling will be used to estimate hazard ratios and corresponding 95% confidence intervals.

The following additional sensitivity analyses will be carried out for overall survival on the ITT population (except as indicated) to evaluate the robustness of the primary analysis results:

log-rank comparisons of treatments on the PP population

stratified log rank analyses, using randomization stratification factors [with hazard ratio estimates from stratified Cox modeling]

Wilcoxon comparisons of treatments

Cox regression model with stepwise selection (p value to enter < 0.25, p-value to remain < 0.15) of model terms where treatment and the prognostic factors (noted below) are candidates for inclusion

univariate analyses to evaluate potential independent prognostic factors using Cox regression

subgroup analyses to examine differences in the effects of treatment in different segments of the study population.

Repeat all analyses (primary and sensitivity) with only patients who enrolled under protocol Version 2 (and later)

Prognostic factors to be examined include: baseline KPS, baseline albumin, ethnicity, geographic location, disease stage at diagnosis, original tumor location, number of prior chemotherapy treatments, prior radiotherapy, prior surgery, time since last treatment, best response on prior treatment, baseline CA 19-9, gender and age.

W. Secondary Efficacy Analyses

Progression Free Survival

PFS is defined as the number of months from the date of randomization to the date of death or progression, whichever occurred earlier (per RECIST 1.1). If neither death nor progression is observed during the study, PFS data will be censored at the last valid tumor assessment.

PFS will be compared between the treatment groups using paired un-stratified log-rank tests. The PFS curves will be estimated using Kaplan-Meier estimates. Estimates of the hazard ratios and corresponding 95% confidence intervals will be obtained using Cox proportional hazard models. Stratified analyses will also be carried

out using the randomization stratification factors. Treatment effects adjusting for stratification variables and other prognostic covariates will be explored. In addition, different censoring and missing data imputing methods may be used to perform sensitivity analyses on PFS. Methodology for the sensitivity analyses will be fully specified in the Statistical Analysis Plan.

The analyses will be performed for ITT, PP and EP populations.

Time to Treatment Failure

Time to treatment failure is defined as time from randomization to either disease progression, death or study discontinuation due to toxicity. Kaplan-Meier analyses as specified for analyses of progression free survival will be performed for time to treatment failure.

The analyses will be performed for ITT, PP and EP populations.

Objective Response Rate

The tumor assessment related to ORR will be determined using RECIST v1.1. If the Sponsor requires an independent review of the radiological assessments to support a new drug application or for any other reason, the response status of all patients may be reviewed by an independent panel of clinicians and may be reviewed by the Sponsor or its designee. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment will take precedence.

Objective response rate (ORR) for each treatment group will be calculated combining the number of patients with a best overall response of confirmed CR or PR per RECIST. The ORR is the best response recorded from randomization until progression or end of study. The number and percentage of patients experiencing objective response (confirmed CR + PR) at the time of analysis will be presented and the 95% confidence interval for the proportion will be calculated. Objective response rates from the treatment arms will be compared using pair-wise Fisher's Exact Tests. The analyses will be performed for ITT, PP and EP populations.

Tumor Marker Response Analysis

CA 19-9 serum levels will be measured within 7 days before the start of treatment (baseline), and subsequently every 6 weeks. Tumor marker response of CA19-9 will be evaluated by the change of CA19-9 serum levels. Response is defined as a decrease of 50% of CA 19-9 in relation to the baseline level at least once during

the treatment period. Only patients with elevated baseline CA 19-9 value (> 30 U/mL) will be included in the calculation of tumor marker response rate.

Patient Reported Outcome Analyses

Analysis of the EORTC-QLQ-C30 questionnaires will be performed in accordance with the EORTC guidelines [22].

Safety Analysis

Treatment emergent adverse events will be presented by treatment arm, by patient, by NCI CTCAE grade and by MedDRA system organ class (SOC). Separate listings will be presented for total adverse events, serious adverse events, adverse events related to the study drugs and Grade 3 and 4 adverse events. Laboratory data will be presented by treatment arm and by visit. Abnormal laboratory values will be assessed according to NCI CTCAE grade, where possible. Evaluation of QTc will be done based upon Fridericia's correction method. CTCAE criteria will be applied to the QTc_F (i.e. Grade 3 = QTc > 500 msec). All the safety analyses will be performed by treatment arm, treatment cycle and week, where appropriate. Overall safety will also be evaluated by grade across cycles, SOC and extent of exposure. Additionally, safety analyses will include a comparison between the treatment arms in all patients in the Safety Population:

- Number of blood transfusions required
- Proportion of patients requiring G-CSF
- Adverse events resulting in dose delay or modification

Pharmacokinetics Analysis

Pharmacokinetic data will be collected on all patients randomized to either of the MM-398 arms. Plasma concentration-time data for MM-398 will be analyzed using population pharmacokinetic methods. Pharmacokinetic parameters will be estimated by Non-Linear Mixed Effects Modeling using NONMEM®, Version 7, Level 1.0 (ICON Development Solutions, Dublin, Ireland). PK parameters will include plasma C_{max}, T_{max}, AUC (area under the concentration curve), clearance, volume of distribution, and terminal elimination half-life. The effects of patient specific factors (age, race, gender, body weight, hepatic and renal function measures, ECOG value, etc.) on pharmacokinetic parameters will be evaluated. Population PK/PD methods will be used to assess the relationships between drug exposure and efficacy and/or toxicity (e.g. neutropenia, diarrhea) parameters. Additional

exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study. Concentration levels of 5-FU will be summarized descriptively.

Endnotes

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein. The disclosure of each and every US, international, or other patent or patent application or publication referred to herein is hereby incorporated herein by reference in its entirety.

Claims

What is claimed is:

1. A method of treating pancreatic cancer in a human patient, the method comprising: administering to the patient an affective amount of liposomal irinotecan, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2.

2. The method of claim 1, wherein the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

3. A method of treating pancreatic cancer in a human patient, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form).

4. The method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

5. The method of claim 3 or claim 4, wherein after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2.

6. The method of any one of the preceding claims, wherein the liposomal irinotecan is administered intravenously over 90 minutes.

7. The method of any one of claims 3-6, wherein the 5-FU is administered intravenously over 46 hours.

8. The method of any one of claims 3-7, wherein the leucovorin is administered intravenously over 30 minutes.

9. The method of any one of the preceding claims, wherein, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

10. The method of any one of the preceding claims, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

11. The method of any one of the preceding claims, wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

12. A formulation of irinotecan for co-administration with 5-fluorouracil (5-FU) and leucovorin in at least one cycle, wherein the cycle is a period of 2 weeks, the formulation of irinotecan is a liposomal formulation of irinotecan, and wherein:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form).

13. The formulation of irinotecan of claim 12 wherein after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2.

14. The formulation of claim 12 or claim 13, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

15. The formulation of any one of claims 12-14, wherein the liposomal irinotecan is administered intravenously over 90 minutes.

16. The formulation of any one of claims 12-15, wherein the 5-FU is administered intravenously over 46 hours.

17. The formulation of any one of claims 12-16, wherein the leucovorin is administered intravenously over 30 minutes.

18. The formulation of any one of claims 12-17, wherein, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

19. The formulation of any one of claims 12-18, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

20. The formulation of any one of claims 12-19 wherein the liposomal formulation of irinotecan is irinotecan sucrose octasulfate salt liposome injection.

21. A method of improving chemotherapy outcomes by increasing tumor vascularity, the method comprising administering to a patient having a tumor an

amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and concomitantly administering an effective amount of at least one anti-cancer agent other than irinotecan to the patient.

22. Irinotecan sucrose octasulfate salt liposome injection for concomitant administration to a patient having a tumor of 1) an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and 2) an effective amount of at least one anti-cancer agent other than irinotecan.

23. A kit for treating pancreatic cancer in a human patient, the kit comprising a dose of liposomal irinotecan and instructions for using liposomal irinotecan in the method of claim 1 or 2.

24. A kit for treating pancreatic cancer in a human patient, the kit comprising a dose of each liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, 5-FU, and leucovorin in the method of claim 3 or 4.

25. The kit of claim 24, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

26. The kit of any one of claims 23-25, wherein the liposomal irinotecan is MM-398.

27. The method of any one of claims 1-11, or the formulation of any one of claims 13-21, wherein the co-administration results in therapeutic synergy or in a positive outcome in the patient, and wherein the positive outcome is pCR, CR, PR, or SD.

Activity of MM-398 (Ls-CPT11) in an Orthotopic Pancreas Tumor Model Expressing Luciferase (L3.6pl).

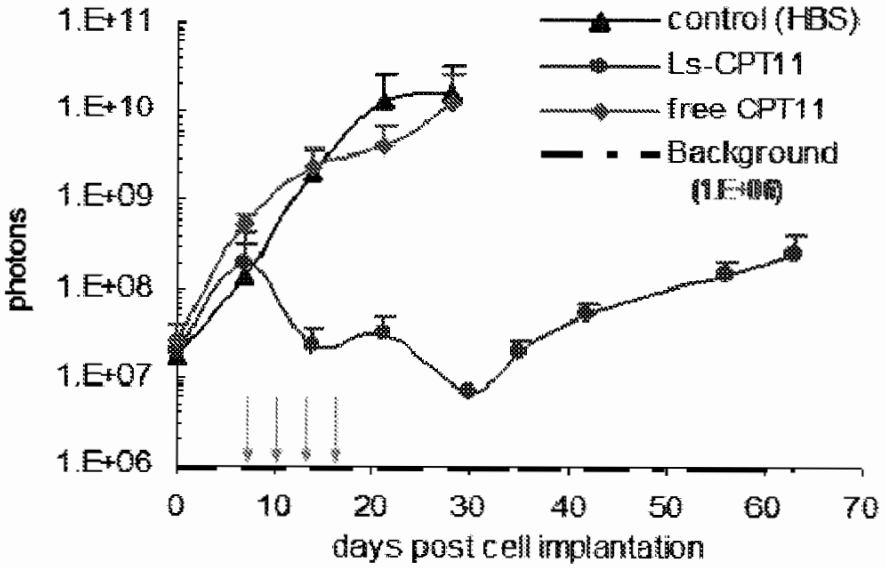


Fig. 1

Accumulation of SN-38 in Tumors Following Treatment with Free Irinotecan or Nanoliposomal Irinotecan (MM-398).

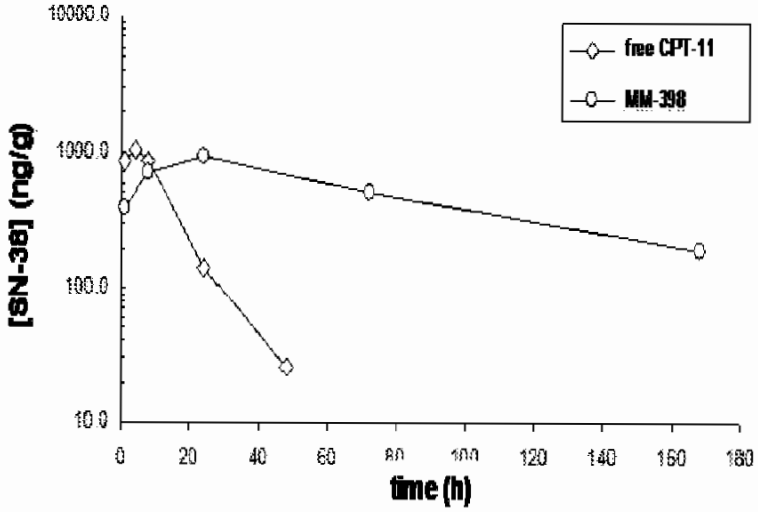


Fig. 2

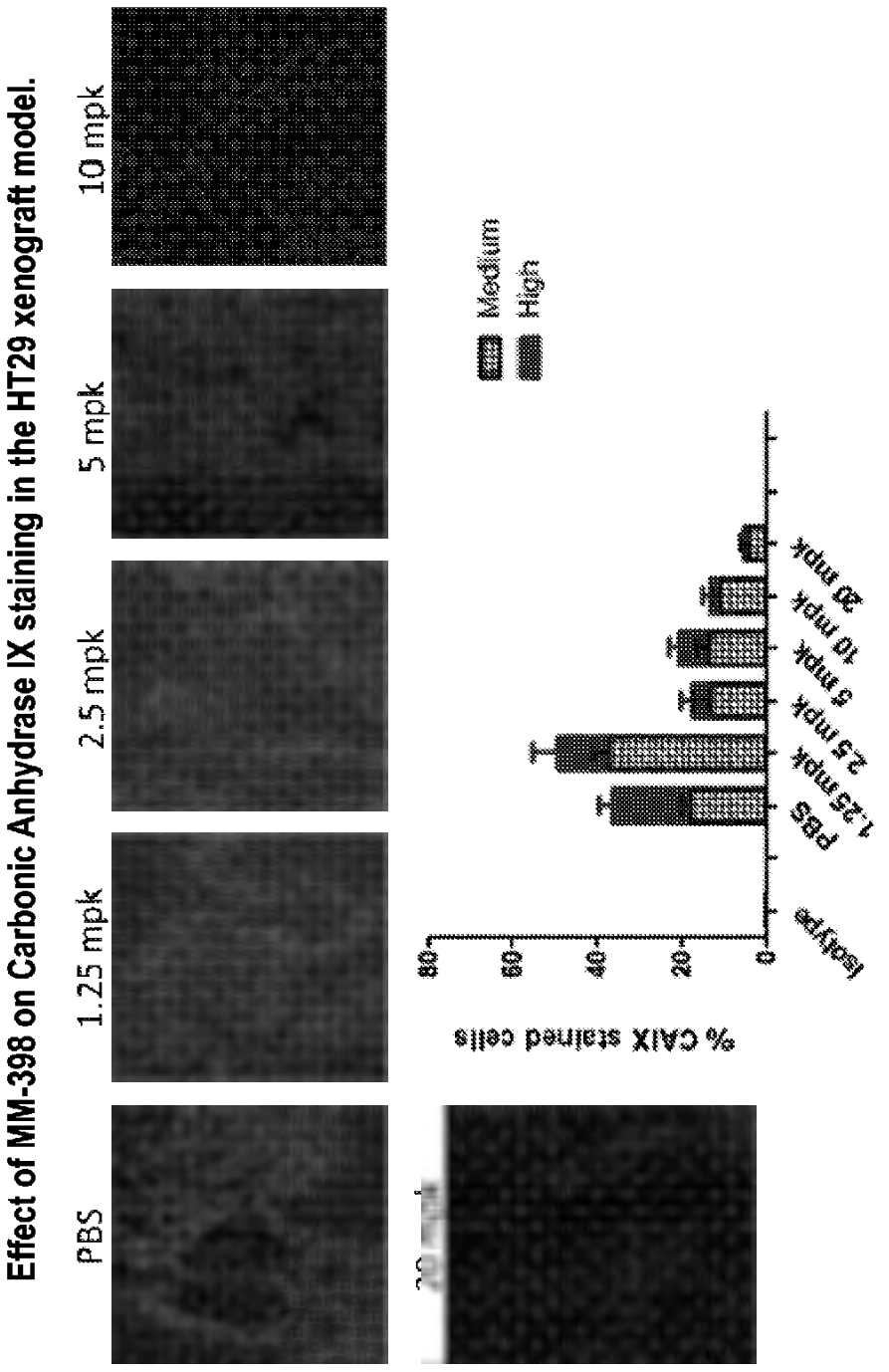

Effect of MM-398 on Carbonic Anhydrase IX staining in the HT29 xenograft model.
PBS
1.25 mpk
2.5 mpk
5 mpk
10 mpk
20 mpk
Medium
High
% CAIX stained cells
0
20
40
60
80
Isotype
PBS
1.25 mpk
2.5 mpk
5 mpk
10 mpk
20 mpk

Fig. 3

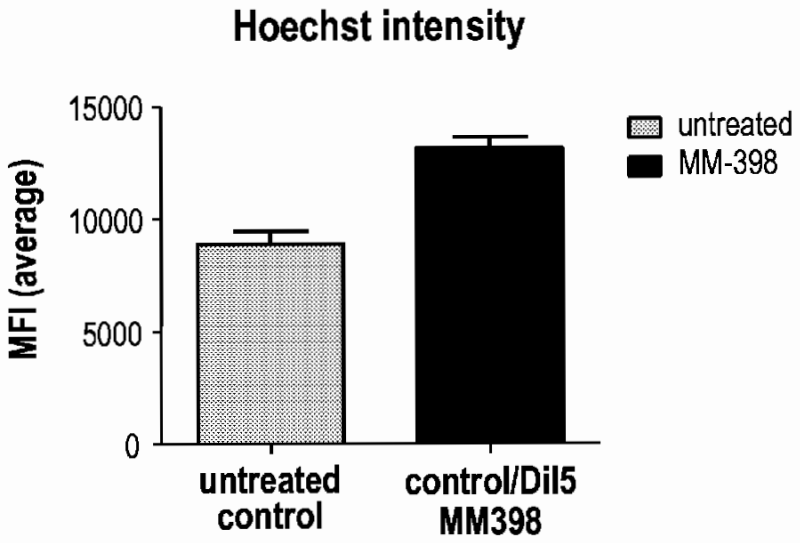

Hoechst intensity
MFI (average)
15000
10000
5000
0
untreated
MM-398
untreated control
control/Dil5 MM398

Fig. 4

MM-398 PK in q3w (irinotecan, liposome + free drug)

Dose (mg/m²) & Study	PEP0203			PEP0201		PEP0206		Camptosar® Package Insert
Parameters	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Campto® 300 (n = 27)	125 mg/m² (Mean)	340 mg/m² (N=6)
C_{max} (ng/mL)	29.93 (± 15.75)	29.16 (± 5.24)	44.05 (± 7.65)	47.94 (± 16.24)	79.4 (± 13.9)	102 (± 17.6)	60.8 (± 36.6)	4.3 (± 1.2)	1.66 (± 0.757)	3.392 (± 0.674)
$t_{1/2}$ (h)	24.02 (± 16.76)	32.69 (± 18.21)	48.11 (± 17.41)	30.65 (± 5.32)	29.5 (± 17.2)	22.2 (± 11.5)	21.2 (± 18.3)	7.7 (± 4.4)	5.8 (± 0.7)	11.7 (± 1.69)
AUC_{0-T} (ng*h/mL)	1,047 (± 1,150)	1,116 (± 818)	2,193 (± 1,017)	1,117 (± 308)	2,835 (± 1,817)	1,945 (± 1,029)	1,651.5 (± 1,412.0)	24.2 (± 7.7)	18.2 (± 3.27)	28.6804 (± 6.6727)
$AUC_{0-\infty}$ (ng*h/mL)	1,114 (± 1,270)	1,211 (± 924)	2,472 (± 1261)	1,261 (± 300)	2,963 (± 1,947)	1,963 (± 1,035)	1,812.2 (± 1,691.9)	26.2 (± 9.9)	"	"
Cl (L/h/m)	0.1249 (± 0.1658)	0.1164 (± 0.0 949)	0.0547 (± 0.0358)	0.1033 (± 0.0469)	0.0991 (± 0.0367)	0.119 (± 0.0703)	0.191 (± 0.268)	12.9 (± 4.7)	13.3 (± 6.01)	13.32 (± 4.69)
V_{ss} (L/m²)	2.6 (± 1.44)	2.93 (± 0.60)	2.63 (± 0.49)	3.16 (± 0.38)	1.8 (± 0.771)	1.97 (± 0.342)	2.23 (± 0.69)	98.5 (± 29.0)	110 (± 48.5)	234 (± 69.6)

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert,
T= 49.5 hours for Camptosar in the PEP0206 study and
T = 169.5 hours for MM-398.

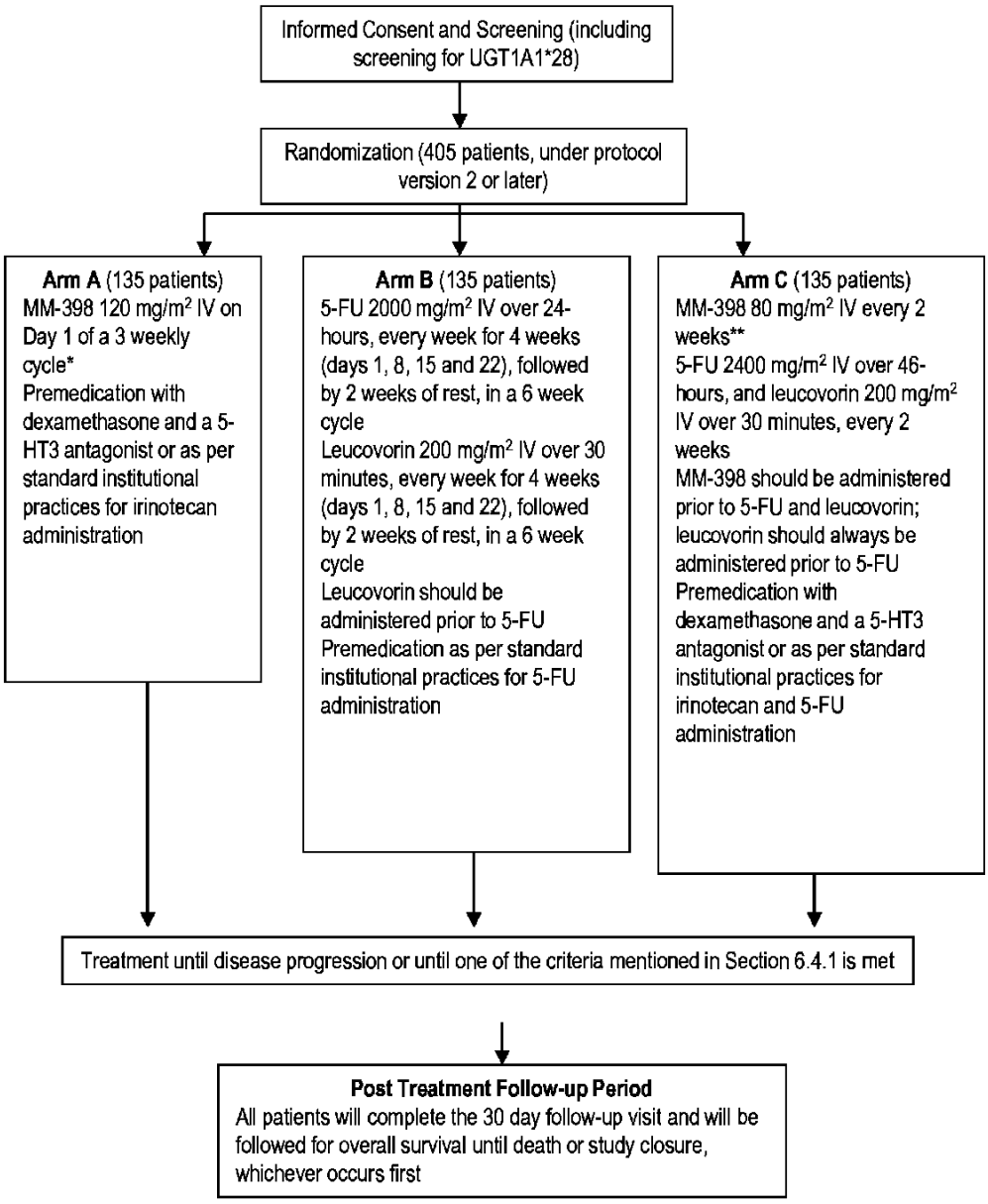
Fig. 5

MM-398 PK in q3w (SN-38)

Dose (mg/m²) & Study	PEP0203			PEP0201		PEP0206		Camptosar Package Insert
Parameter	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Campto® 350 (n = 27)	125 mg/m² (n = 64)	347 mg/m² (n = 6)
C_{max} (ng/mL)	7.02 (± 5.84)	7.98 (± 4.39)	7.39 (± 1.69)	16.64 (± 9.36)	9.3 (± 3.5)	14.3 (± 6.16)	8.79 (± 8.68)	44.1 (± 28.2)	26.3 (± 11.9)	56.0 (± 28.2)
$t_{1/2}$ (h)	183.81 (± 172.3)	53.75 (± 15.6)	73.41 (± 18.3)	25.23 (± 6.53)	75.4 (± 43.8)	52.0 (± 32.8)	88.8 (± 114.6)	22.8 (± 10.9)	10.4 (± 3.1)	21.0 (± 4.3)
AUC_{0-T} (ng·h/mL)	367.40 (± 227)	354.77 (± 145)	551.40 (± 351.8)	357.60 (± 155.7)	710 (± 395)	1,160 (± 969)	467 (± 310)	361 (± 125)	229 (± 108)	474 (± 245)
$AUC_{0-\infty}$ (ng·h/mL)	1,373.3 (± 1,119)	502.15 (± 153)	844.28 (± 444)	474.00 (± 209)	997 (± 680)	1,429 (± 1,134)	879 (± 1,435)	440 (± 162)	-	-

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert,
T= 49.5 hours for Camptosar in the PEP0206 study and
T = 169.5 hours for MM-398.

Fig. 6



* Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm A, will receive the first cycle of therapy at a reduced dose of 80 mg/m2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased in increments of 20 mg/m2, up to a maximum of 120 mg/m2.

** Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m2.

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/045495

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/4745 A61K31/513 A61K31/517 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Study of MM-398 Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer", , 11 December 2011 (2011-12-11), pages 1-3, XP055075223, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01494506/2011_12_16 [retrieved on 2013-08-14] the whole document ----- -/--	1,10-20, 23,26,27

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2013	22/08/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Haider, Ursula

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chang-Sung Tsai ET AL: "Nanovector-based therapies in advanced pancreatic cancer", Journal of Gastrointestinal Oncology, 1 September 2011 (2011-09-01), pages 185-194, XP055075231, DOI: 10.3978/j.issn.2078-6891.2011.034 Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3397610/pdf/jgo-02-03-185.pdf [retrieved on 2013-08-14]	1,6, 10-27
Y	page 189, right-hand column, paragraph 2	2-9

Y	J. M. HOSKINS ET AL: "UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters", JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE, vol. 99, no. 17, 5 September 2007 (2007-09-05), pages 1290-1295, XP055022025, ISSN: 0027-8874, DOI: 10.1093/jnci/djm115 the whole document	2

Y	HEDIA BRIXI-BENMANSOUR ET AL: "Phase II study of first-line FOLFIRI for progressive metastatic well-differentiated pancreatic endocrine carcinoma", DIGESTIVE AND LIVER DISEASE, W.B. SAUNDERS, GB, vol. 43, no. 11, 1 July 2011 (2011-07-01), pages 912-916, XP028296448, ISSN: 1590-8658, DOI: 10.1016/J.DLD.2011.07.001 [retrieved on 2011-07-07] page 915, right-hand column, paragraph 5	2-9

X,P	JEFFREY R INFANTE ET AL: "Phase I and pharmacokinetic study of IHL-305 (PEGylated liposomal irinotecan) in patients with advanced solid tumors", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 70, no. 5, 2 September 2012 (2012-09-02), pages 699-705, XP035132528, ISSN: 1432-0843, DOI: 10.1007/S00280-012-1960-5 the whole document	1-27

	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/045495

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	"Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer", , 9 August 2012 (2012-08-09), pages 1-3, XP055075259, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01494506/2012_08_09 [retrieved on 2013-08-14] the whole document -----	1-27

1

Bibliographic Data

Application No: 15809815

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: Celeste Roney (Examiner's Signature) | (Initials)

Title: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/10/2017	424	1612	263266-421428
RULE			

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Helen Lee, Arlington, MA, UNITED STATES

CONTINUING DATA

This application is a CON of 15241106 08/19/2016

15241106 has PRO of 62343313 05/31/2016

15241106 has PRO of 62323245 04/15/2016

15241106 has PRO of 62302341 03/02/2016

15241106 has PRO of 62281473 01/21/2016

15241106 has PRO of 62273244 12/30/2015

15241106 has PRO of 62216736 09/10/2015

15241106 has PRO of 62208209 08/21/2015

FOREIGN APPLICATIONS

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12/13/2017

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FILING FEE RECEIVED

$1,600

Importance of sequence in chemotherapy administration

Is sequencing important when administering chemotherapy on the same day?

WEST Search History for Application 15809815

Creation Date: 2018022108:43

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
irinotecan with oxaliplatin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	14417	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin) and leucovorin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	7488	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin) and fluorouracil	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	7333	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin and fluorouracil) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4086	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin and fluorouracil and liposome) and pancreas or pancreatic	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	194019	ADJ	YES		02-21-2018
irinotecan with oxaliplatin with leucovorin with fluorouracil	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	5104	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil) and pancreas	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	2596	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1571	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas and liposome) and cycle	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1312	ADJ	YES		02-21-2018

(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas and liposome and cycle) and immunoliposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	71	ADJ	YES		02-21-2018

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
west and palm searches	02/21/2018	CR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
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PUBLICATION NOTICE

153749
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125 Cambridge Park Drive
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Cambridge, MA 02140

OC000000098223514

Title: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

Publication No.US-2018-0078556-A1
Publication Date:03/22/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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McNeill Baur PLLC/Ipsen
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125 Cambridge Park Drive
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Eliel BAYEVER et al.	Group Art Unit: 1621
Application No.: 15/809,815	Examiner: Celeste A. Roney
Filed: November 10, 2017	Confirmation No.: 5137
For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Via EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Roney:

In reply to the Office Action mailed March 6, 2018, the period for response having been extended to August 6, 2018, by a request for extension of 2 month and fee payment filed concurrently herewith, please amend the above-identified application as follows:

Amendments to the Claims begin at page 2.

Remarks begin at page 6.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application. Please amend the claims as follows:

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60~~ or 85~~ mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

2. (Canceled)

3. (Canceled)

4. (Original) The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

5. (Original) The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

6. (Original) The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

7. (Original) The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

8. (Original) The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

9. (Original) The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. (Original) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

11. (Original) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

12. (Currently Amended) The method of claim [[2]]1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes~~, and the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting~~ composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

13. (Currently Amended) The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, ~~and~~ leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

14. (Currently Amended) The method of claim [[3]]19, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes~~, and the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting~~ composed

of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

15. (Currently Amended) The method of claim 14, wherein the liposomal irinotecan, oxaliplatin, ~~and~~ leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

16. (Canceled)

17. (Canceled)

18. (Currently Amended) The method of claim [[17]]19, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

19. (Original) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

20. (Canceled)

21. (New) The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

22. (New) The method of claim 14, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

REMARKS

I. Status of Claims

Following entry of this amendment, claims 1, 4-15, 18, 19, 21, and 22 are pending in the application. Claims 21 and 22 have been added and claims 2, 3, 16, 17, and 20 have been canceled without prejudice or disclaimer. Applicant expressly reserves the right to pursue the subject matter of those claims in the future. Claim 1 was amended to no longer recite 85 mg/m^2 oxaliplatin and claims 12-15 and 18 were amended to adjust claim dependencies and to even more clearly recite the subject matter being claimed. Support for the amendments and new claims 21 and 22 can be found throughout the specification and originally filed claims, for example at original claims 13 and 15 and at page 29, line 22. The amendments and new claims add no new matter.

II. Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1-3, 5-8, 10, 16, and 19 under 35 U.S.C. § 103 as allegedly being obvious over WO 2013/188586 ("Bayever") in view of Conroy et al., N Engl J Med., 364(19):1817-25, 2011) ("Conroy"). Office Action at p. 2. The Examiner asserted that Bayever discloses treatment of metastatic pancreatic cancer comprising "co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan)," a dose of 2400 mg/m^2 5-fluorouracil, and a dose of 200 mg/m^2 l form or 400 mg/m^2 l+d form leucovorin for at least one cycle of two weeks. *Id.* at pp. 2-3. The Examiner also alleged that Conroy disclosed treatment of metastatic pancreatic cancer with oxaliplatin, irinotecan, leucovorin, and fluorouracil. *Id.* at p. 3. Furthermore, the Examiner alleged that "it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment" and

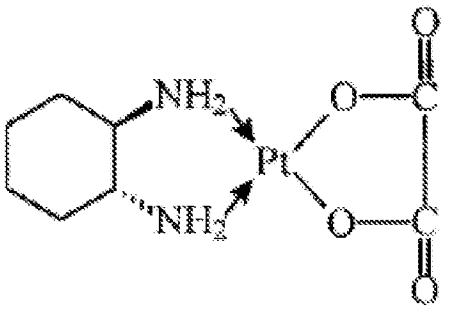
that "[a]n ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy… ." *Id.*

Applicant respectfully traverses. Solely to expedite prosecution and without acquiescing to the rejection, Applicant canceled claims 2, 3, and 16 and amended claim 1 to recite "60 mg/m^2 oxaliplatin." Bayever discloses treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2), in combination with leucovorin (e.g., 400 mg/m^2 *l* + *d* form) and 5-fluorouracil (e.g., 2,400 mg/m^2) to a patient once every two weeks. Conroy discloses treatment of patients with first-line metastatic pancreatic cancer by administering a different combination of therapeutic agents in different doses: Conroy administers a combination of 85 mg/m^2 oxaliplatin, 180 mg/m^2 non-liposomal irinotecan, 400 mg/m^2 leucovorin, 400 mg/m^2 fluorouracil as a bolus injection followed by 2400 mg/m^2 fluorouracil as a continuous infusion once every two weeks. Neither Bayever nor Conroy, however, teaches or suggests (solely or in combination) the claimed methods of treatment, including co-administering "60 mg/m^2 oxaliplatin," as recited in independent claims 1 and 19.

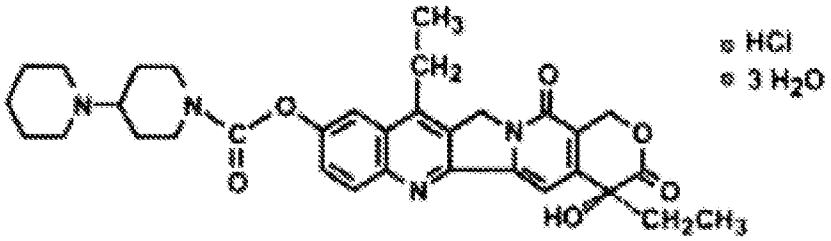
First, the Examiner has failed to establish a *prima facie* case of obviousness at least with respect to the claimed co-administration of a dose of "60 mg/m^2 oxaliplatin." The Office "must provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention" such as "[s]ome teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." MPEP §2143. The Examiner asserted that original claim 2, which recited a dose of 60 mg/m^2 oxaliplatin, "is rendered prima facie obvious because Bayever disclosed active agents

administered at 60 mg/m^2 (e.g. irinotecan) once per two weeks." Office Action at p. 4. However, the Examiner failed to provide a reasoned explanation as to why a person of ordinary skill in the art would have chosen a dose of oxaliplatin based on the dose of liposomal irinotecan described in Bayever. For example, the Examiner has not presented any evidence as to how or why a dose of one compound would have any bearing on the dose of a compound having a completely different chemical structure, that is associated with a completely different class of antineoplastic agents, and that is formulated in a completely different manner.

No *prima facie* case of obviousness exists in view of the cited art for at least the reason that a person of ordinary skill in the art would not have been motivated to select a 60 mg/m^2 dose of oxaliplatin based on the 60 mg/m^2 dose of liposomal irinotecan described in Bayever. Oxaliplatin and liposomal irinotecan are different compounds from different classes of antineoplastic agents. Oxaliplatin is a platinum-based drug having the following chemical structure:



See Oxaliplatin Package Insert (SB08 Reference No. 1) at section 11. The active derivatives of oxaliplatin form DNA crosslinks. *See id* at p. 27, Section 12.1. In contrast, irinotecan hydrochloride trihydrate is a topoisomerase 1 inhibitor that has the following chemical structure:



See Camptosar® Package Insert (SB08 Reference No. 2) at section 11. Furthermore, the oxaliplatin formulation of Conroy does not appear to be encapsulated in a liposome as are the irinotecan formulations described in Bayever.

In sum, a person of ordinary skill in the art would not have been motivated to co-administer a dose of 60 mg/m^2 of oxaliplatin based on the dose of a compound having a completely different chemical structure, that is associated with a completely different class of antineoplastic agents, and that is formulated in a completely different manner. Accordingly, the pending claims would not have been *prima facie* obvious for at least the reason that neither Bayever nor Conroy teaches or suggests (solely or in combination) co-administering "60 mg/m^2 oxaliplatin," as recited in independent claims 1 and 19.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over Bayever in view of Conroy.

The Examiner rejected claims 4, 9, and 18 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy and further in view of Fleming et al. found at http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/ ("Fleming"). Office Action at pp. 4-5. The Examiner alleged Fleming disclosed at the last sentence of the first paragraph that "the sequence of various

chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics." *Id.* at p. 5. The Examiner alleged that in view of Fleming, an ordinarily skilled artisan would have been motivated to vary the order of administration of the combined methods of Bayever and Conroy. *Id.* at pp. 5-6.

Applicant respectfully traverses. As an initial matter, Applicant traverses because the Examiner has not provided a complete copy of Fleming and the entire article is not directly available at the website address identified by the Examiner absent providing a login and password. The copy of Fleming provided by the Examiner simply provides the title, "Importance of sequence in chemotherapy administration" and poses the question, "Is sequencing important when administering chemotherapy on the same day?" The disclosure from Fleming that the Examiner used as the basis of the rejection is not included in the copy provided and is not readily available to Applicant through the website address. Hence, Applicant has not been provided the opportunity to fully consider the reference or the Examiner's rejection. Applicant respectfully requests that the Examiner provide a copy of Fleming in its entirety.

Applicant also traverses for at least the reasons discussed above with respect to claims 1 and 19, from which claims 4, 9, and 18 depend. As discussed, a person of ordinary skill in the art would not have been motivated to co-administer a dose of 60 mg/m^2 of oxaliplatin based on the dose of a compound having a completely different chemical structure, that is associated with a completely different class of antineoplastic agents, and that is formulated in a completely different manner. Accordingly, claims 4, 9, and 18 would not have been *prima facie* obvious for at least the reason that neither Bayever nor Conroy teaches or suggests (solely or in combination) co-administering "60 mg/m^2 oxaliplatin," as recited in independent claims 1 and 19.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over Bayever in view of Conroy and further in view of Fleming.

The Examiner rejected claims 11-15, 17, and 20 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy, as evidenced by WO 2016/094402 ("Bayever II"). *Id.* at p. 6. The Examiner alleged that while "Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12, 17 and 20," Bayever II "evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE." The Examiner also alleged that claims 13-15, 17 and 20 are rendered obvious because of the administration durations and cycles disclosed in Bayever. *Id.* at p. 7.

Applicant respectfully traverses. Solely to expedite prosecution and without acquiescing to the rejection, Applicant canceled claims 17 and 20. Claims 11-15 and 21 and 22 depend from either claim 1 or 19, which recite "60 mg/m^2 oxaliplatin." As discussed above, a person of ordinary skill in the art would not have been motivated to co-administer a dose of 60 mg/m^2 of oxaliplatin based on the dose of a compound having a completely different chemical structure, that is associated with a completely different class of antineoplastic agents, and that is formulated in a completely different manner. Accordingly, claims 4, 9, and 18 would not have been *prima facie* obvious for at least the reason that neither Bayever nor Conroy teaches or suggests (solely or in combination) co-administering "60 mg/m^2 oxaliplatin," as recited in independent claims 1 and 19.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over Bayever in view of Conroy as evidenced by Bayever II.

III. Nonstatutory Double Patenting Rejections

The Examiner rejected claims 1-20 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-18 of U.S. Patent No. 9,492,442 ("the '442 Patent") or claims 1-20 of copending Application No. 15/652,513[1] ("the '513 Application"), in view of Conroy. *Id.* at pp. 8-9. The Examiner alleged that the "issued [and copending] claims recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin." *Id.* at pp. 8-9. The Examiner further alleged that "it would have been prima facie obvious to have used oxaliplatin in the issued [and copending] method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vivo*." *Id* at pp. 9-10.

Applicant respectfully traverses. Solely to expedite prosecution and without acquiescing to the rejection, Applicant canceled claims 2, 3, 16, 17, and 20 and amended claim 1 to recite "60 mg/m^2 oxaliplatin." At least one difference between the pending claims and claims 1-18 of the '442 patent or claims 1-20 of the '513 Application is that the instant pending claims recite (directly or indirectly) administration of 60 mg/m^2 oxaliplatin. Coadministration of a dose of 60 mg/m^2 oxaliplatin would not have been an obvious variation of any of claims 1-18 of the '442 Patent or claims 1-20 of the '513 Application for at least the reasons discussed below.

[1] U.S. Patent Application No. 16/012,351 ("the '351 Application), which was filed on June 19, 2018, is a continuation of the '513 Application. Pending claims 1-20 of the '351 Application are the same as claims 1-20 of the '513 Application, which has since gone abandoned. Any reference to or discussion of claims 1-20 of the '513 Application also applies to claims 1-20 of the '351 Application as they are currently pending.

First, the Examiner's rejection falls short of presenting a proper nonstatutory double patenting rejection under the obviousness analysis. "Any nonstatutory double patenting rejection made under the obviousness analysis should make clear:

(A) The differences between the inventions defined by the conflicting claims – a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent." MEPEP § 804 II. B. 2. The Examiner's obviousness allegation merely attempted to address administration of oxaliplatin but failed to include any reason as to why a person of ordinary skill in the art would conclude that co-administering a dose of 60 mg/m^2 oxaliplatin would have been an obvious variation of any one of claims 1-18 of the '442 Patent or claims 1-20 of the '513 Application.

As discussed above, a person of ordinary skill in the art would not have been motivated to co-administer a dose of 60 mg/m^2 oxaliplatin based the teachings of Conroy or based on the "60-80 mg/m^2 dose of liposomal irinotecan composition" recited in issued independent claims 1 and 10 of the '442 Patent or independent claims 1 and 10 of the '513 Application. Oxaliplatin and liposomal irinotecan have different chemical structures and are associated with different classes of antineoplastic agents. And the oxaliplatin formulation of Conroy does not appear to be liposomal. A person of ordinary skill in the art would not have been motivated to use a dose of 60 mg/m^2 oxaliplatin based on the dose of a compound having a completely different chemical structure, that is associated with a completely different class of antineoplastic agents, and that is formulated in a completely different manner. Accordingly, the pending claims are not obvious variations of issued claims 1-18 of the '442 Patent or claims 1-20 of the '513 Application.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-18 of the '442 Patent and claims 1-20 of the '513 Application, in view of Conroy.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

MCNEILL BAUR PLLC.

Dated: August 6, 2018

By: /Mary R. Henninger/
Mary R. Henninger, PhD
Reg. No. 56,992
404-891-1400

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 01208-0007-01US

Application Number: 15/809,815

Filed: 2017-11-10

For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

Art Unit: 1612

Examiner: Celeste A. Roney

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☑	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 600
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 56992.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Mary R. Henninger/ — Signature

August 6, 2018 — Date

Mary R. Henninger — Typed or printed name

(404) 891-1400 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Inventors:	Group Art Unit: 1612
Eliel BAYEVER et al.	Examiner: Celeste A. Roney
Application No.: 15/809,815	Confirmation No.: 5137
Filed: November 10, 2017.	
Title: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

VIA EFS WEB
Commissioner of Patents
Mail Stop - Amendment
P.O. Box 1450
Arlington, VA 22313-1450

Commissioner:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), Applicant brings to the attention of the Examiner the documents listed on the enclosed IDS Form PTO/SB/08. This Information Disclosure Statement is being filed after the mailing of an Office Action on the merits, but to Applicant's knowledge, prior to the mailing of a Final Office Action, *ex parte Quayle* Action, or Notice of Allowance. This Information Disclosure Statement is accompanied by $240, as required by 37 C.F.R. §1.97(c).

The listed documents are of record in parent application No. 15/241,106, and accordingly copies are not enclosed.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or

constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

Applicant further reserves the right to take appropriate action to establish the patentability of the claimed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

MCNEILL BAUR PLLC.

Dated: August 6, 2018

By: /Mary R. Henninger/
Mary R. Henninger, PhD
Reg. No. 56,992
404-891-1400

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Bayever
Art Unit	1612
Examiner Name	RONEY, Celeste A
Attorney Docket Number	01208-0007-01US

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15809815
	Filing Date	2017-11-10
	First Named Inventor	Bayever
	Art Unit	1612
	Examiner Name	RONEY, Celeste A
	Attorney Docket Number	01208-0007-01US

	1	OXALIPLATIN label, revised November 2013.
	2	CAMPTOSAR label, revised December 2014.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15809815
	Filing Date	2017-11-10
	First Named Inventor	Bayever
	Art Unit	1612
	Examiner Name	RONEY, Celeste A
	Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2018-08-06
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	15809815
Filing Date:	10-Nov-2017
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Filer:	Mary Rucker Henninger/richard king
Attorney Docket Number:	263266-421428

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**840**

Electronic Acknowledgement Receipt

EFS ID:	33388506
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/richard king
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	263266-421428
Receipt Date:	06-AUG-2018
Filing Date:	10-NOV-2017
Time Stamp:	18:33:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$840
RAM confirmation Number	080718INTEFSW18352600
Deposit Account	506488
Authorized User	Richard King

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2018-08-06_237IBL_P7_US-A_01208-0007-01US_Resonse_to_NFOA.pdf	193966 bdf6b6f286656dac1ea6054fb60a640ac0ddc392	yes	14

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	14

Warnings:

Information:

2	Extension of Time	2018-08-06_237IBL_P7_US-A_01208-0007-01US_EOT.pdf	164995 700142084719723a195a994bcfd35af02677d4d0	no	2

Warnings:

Information:

3	Transmittal Letter	2018-08-06-237IBL_P7_US-A_01208-0007-01US_IDS_Transmittal.pdf	115307 7c9abc6a39ba6f0dc06484b45c1c31e66b7c4589	no	2

Warnings:

Information:

4	Information Disclosure Statement (IDS) Form (SB08)	2018-08-06_237IBL_P7_US-A_01208-0007-01US_SB08.pdf	612252 297027295e6a3fafeb75bc82285ff2f2e229106c	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

5	Fee Worksheet (SB06)	fee-info.pdf	32771 8ad7e963a506bcedb280a8958dacdce1a1c7b08c	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1119291	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/809,815	Filing Date 11/10/2017	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/06/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0	X $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
VICTOR BARLOW

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	263266-421428	5137

153749 7590 09/11/2018

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/11/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/809,815	Applicant(s) Bayever et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 06 August 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,4-15,18-19 and 21-22 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,4-15,18-19 and 21-22 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 8/6/18.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED CORRESPONDENCE

Previous Rejections

Applicant's arguments, filed 8/6/18, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 5-8, 10 and 19 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Alcindor et al (Curr Oncol, 2011, 18(1), 18-25).

Bayever et al disclosed a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan). Bayever further disclosed 5-fluorouracil at a dose of 2400 mg/m^2 and leucovorin (*l* form administered at 200 mg/m^2 or the *l*+*d* racemic form administered at 400 mg/m^2). The method comprised

at least one cycle of administration, wherein the cycle was a period of two weeks (page 3, last full paragraph).

In one embodiment, Bayever's population was patients undergoing treatment for metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10).

Bayever did not disclose oxaliplatin, as recited in claim 9.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity in vitro (page 1818, left column, second paragraph).

Conroy did not disclose that the irinotecan was liposomal irinotecan.

Since Bayever disclosed treating metastatic pancreatic carcinoma with 5-fluorouracil and irinotecan, it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment. An ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity in vitro, as taught by Conroy (Conroy, page 1818, left column, second paragraph).

Regarding the claim 1 limitation of 60 mg/m^2 oxaliplatin, the combination of Bayever (e.g., Bayever taught 85 mg/m^2 oxlaplatin at the abstract), though not silent the claimed amount of oxaliplatin, does not specifically teach 60 mg/m^2 oxaliplatin.

However, Alcindor taught that early studies of the development of oxlaliplatin recognized a maximally efficient dose range of 45-67 mg/m^2 (Alcindor at section 6.1, 2nd pargraph). It would have been prima facie obvious to one of ordinary skill in the art to have adjusted the dosage of oxaliplatin, and said artisan would have been so motivated because Alcindor also recognized adverse reactions of oxaliplatin on the hematopoietic, gastrointestinal and peripheral nervous systems (Alcindor at sections 4.1-4.3).

As such, oxlaplatin, and its amount, is recognized to have different effects (greater or less toxicity, as taught by Alcindor and discussed above) with changing amounts used. Thus, the general condition (the dosage) is known and the amount of this ingredient is recognized to be result effective. Therefore, result effective variables can be optimized by routine experimentation, and it would have been prima facie obvious to have optimized the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Alcindor.

The instant claim 1 recites 60 mg/m^2 oxaliplatin. Alcindor taught 45-67 mg/m^2 oxaliplatin. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

The combination of Bayever, Conroy and Alcindor reads on claims 1 and 19.

Claims 5-6 and 8 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal

irinotecan was administered intravenously over 90 minutes, and that leucovorin was administered prior to 5-FU (page 12, section IV).

Claim 7 is rendered prima facie obvious because Bayever disclosed that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle), because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Claim 10 is rendered prima facie obvious because Bayever disclosed irinotecan sucrose octasulfate liposomal irinotecan, where the irinotecan was entrapped within the liposome, at page 4, and the last paragraph.

Response to Arguments

Applicant's arguments filed 3/6/18 have been fully considered but they are not persuasive.

In response to the Applicant's argument that neither Bayever nor Conroy teach the limitation of 60 mg/m^2 oxaliplatin, the Examiner responds that Bayever and Conroy were not relied upon to teach said limitation. The newly recited Alcindor et al teaches 45-67 mg/m^2 oxaliplatin, which overlaps the claimed amount.

Applicant's arguments over claim 2 are rendered moot since claim 2 is not currently pending.

In response to the Applicant's arguments that an ordinarily skilled artisan would not have been motivated to have selected a dosage of 60 mg/m^2 oxaliplatin, the Examiner disagrees. This is because Alcindor teaches that a dose range of 45-67 mg/m^2 oxaliplatin is known in the art. An ordinarily skilled artisan would have been motivated to have adjusted the dosage of oxaliplatin because adverse effects of oxaliplatin on the hematopoietic, gastrointestinal and peripheral nervous systems are also known in the art.

Further, the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation, and as such, an ordinarily skilled artisan would have been motivated to have adjusted and optimized a known variable (e.g., oxaliplatin dosage).

Claims 4, 9 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011,1817) further in view of Alcindor et al (Curr Oncol, 2011, 18(1), 18-25), and further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy and Alcindor, has been discussed above.

Additionally, Bayever disclosed that prior to each administration of liposomal irinotecan, the patient was pre-medicated with dexamethasone (e.g. corticosteroid) and another anti-emetic (page 4, fourth embodiment from the top of the page).

Further, Conroy disclosed that a second active agent was given two hours after a first active agent (e.g., leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose oxaliplatin administration after liposomal irinotecan, as recited in claims 4 and 18; liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming disclosed that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy disclosed administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration.

An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Response to Arguments

Applicant's arguments filed 3/6/18 have been fully considered but they are not persuasive.

In response to the Applicant's argument that Fleming was not provided in its entirety, the Examiner responds that Fleming, in its entirety, is provided with this communication.

Claims 11-15 and 21-22 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817), further in view of Alcindor et al (Curr Oncol, 2011, 18(1), 18-25), and as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever (2013), in view of Conroy and Alcindor, has been discussed above.

Although, Bayever (2013) disclosed MM-398 liposome (at page 4, last paragraph and as discussed above), Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12 and 21-22.

However, Bayever (2016) evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE (page 30, section describing the drug product).

Thus, it is reasonable to assume that Bayever's (2013) MM-398 contained irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.

Claims 13-15 and 21-22 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes; liposomal irinotecan was administered prior to leucovorin; leucovorin was administered prior to 5-FU (page 12, section IV). Further, Bayever disclosed that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration.

For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28-day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Response to Arguments

Applicant's arguments filed 3/6/18 have been fully considered but they are not persuasive.

In response to the Applicant's argument that the cited art does not teach the claimed dosage of oxaliplatin, the Examiner disagrees, as the newly recited Alcindor reads on said limitation.

Nonstatutory Double Patenting

A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably

distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more

information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 4-15, 18-19 and 21-22 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 9,492,442, in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Alcindor et al (Curr Oncol, 2011, 18(1), 18-25).

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the method of treatment except for the administration of oxlaliplatin. The instant claims require oxaliplatin, and such an ingredient is not recited by the issued claims.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity in vitro (page 1818, left column, second paragraph).

Alcindor taught that early studies of the development of oxlaliplatin recognized a maximally efficient dose range of 45-67 mg/m^2 (Alcindor at section 6.1, 2nd pargraph).

Thus, it would have been prima facie obvious to have used oxaliplatin in the issued method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro*.

Response to Arguments

Applicant's arguments filed 3/6/18 have been fully considered but they are not persuasive.

In response to the Applicant's argument that a dosage of 60 mg/m^2 oxaliplatin would not have been obvious to the ordinarily skilled artisan, the Examiner disagrees. This is because Alcindor teaches oxaliplatin dosages that are well known in the art. As such, a skilled artisan would be motivated, and guided, by the art to follow dosage regimens that are well known in the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7 AM-5 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

Notice of References Cited	Application/Control No. 15/809,815	Applicant(s)/Patent Under Reexamination Bayever et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Alcindor et al, Curr Oncol, 2011, 18(1), 18-25
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
west and palm searches	02/21/2018	CR
west and palm searches	09/02/2018	CR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

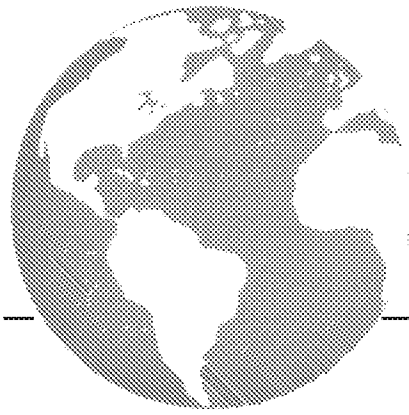
WEST Search History for Application 15809815

Creation Date: 2018090208:05

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
irinotecan with oxaliplatin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	14417	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin) and leucovorin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	7488	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin) and fluorouracil	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	7333	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin and fluorouracil) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4086	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin and leucovorin and fluorouracil and liposome) and pancreas or pancreatic	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	194019	ADJ	YES		02-21-2018
irinotecan with oxaliplatin with leucovorin with fluorouracil	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	5104	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil) and pancreas	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	2596	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1571	ADJ	YES		02-21-2018
(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas and liposome) and cycle	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1312	ADJ	YES		02-21-2018

(irinotecan with oxaliplatin with leucovorin with fluorouracil and pancreas and liposome and cycle) and immunoliposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	71	ADJ	YES		02-21-2018
2013188586.pn.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4	ADJ	YES		03-03-2018
2016094402.pn.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	5	ADJ	YES		03-03-2018
pancreatic adj2 cancer with (irinotecan and oxaliplatin and leucovorin and fluorouracil)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	68	ADJ	YES		03-03-2018
(pancreatic adj2 cancer with (irinotecan and oxaliplatin and leucovorin and fluorouracil)) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	51	ADJ	YES		03-03-2018
pancreas with irinotecan	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	128	ADJ	YES		09-02-2018
(pancreas with irinotecan) and oxaliplatin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	103	ADJ	YES		09-02-2018
(pancreas with irinotecan and oxaliplatin) and leucovorin	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	85	ADJ	YES		09-02-2018
(pancreas with irinotecan and oxaliplatin and leucovorin) and fluorouracil	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	82	ADJ	YES		09-02-2018
(pancreas with irinotecan and oxaliplatin and leucovorin and fluorouracil) and liposome	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	32	ADJ	YES		09-02-2018



Oxaliplatin: a review in the era of molecularly targeted therapy

T. Alcindor MD and N. Beauger PhD MBA*

ABSTRACT

Objective

To review preclinical and clinical data for oxaliplatin in the current context of molecularly targeted therapy.

Methods of Study Selection

We searched the PubMed and PubChem databases by combining the search terms "oxaliplatin" or "platinum" or both, with "clinical trials," "pharmacokinetics," and "pharmacodynamics."

Data Extraction and Synthesis

Oxaliplatin has a complicated pharmacokinetic profile, with activity against digestive cancers in particular. It has several mechanisms of action, but cancer cells can develop resistance. Real or potential synergism has been observed when oxaliplatin is combined with other cytotoxic agents or molecularly targeted agents. Peripheral neuropathy is a prominent toxic effect.

Conclusions

Oxaliplatin lends itself to further clinical research in combination with molecularly targeted therapy.

KEY WORDS

Oxaliplatin, targeted therapy, chemotherapy, mechanism of action

1. INTRODUCTION

The advent of molecularly targeted anticancer therapy could cause a certain lack of interest in the development of novel conventional cytotoxic drugs. However, molecularly targeted agents have not shown any curative properties when administered as monotherapy. In that regard, there is hope in combining molecularly targeted anticancer therapy with conventional cytotoxic chemotherapy. Such combinations can come about only through rational design of clinical trials, taking into account the pharmacology and clinical development of the drugs involved. It is therefore worthwhile revisiting classical chemotherapy agents, because this renewed knowledge could provide a foundation for future trials.

Oxaliplatin is the newest platinum derivative in standard chemotherapy. Here, we review oxaliplatin from the pharmacologic and drug development perspectives, and we comment on possible associations of this drug with molecularly targeted therapy.

2. CHEMICAL AND PHYSICAL PROPERTIES AND BIOTRANSFORMATION

Oxaliplatin differs from cisplatin in that the amine groups of cisplatin are replaced by diaminocyclohexane (DACH). The molecular weight of oxaliplatin is 397.3. It is slightly soluble in water, less so in methanol, and almost insoluble in ethanol and acetone [1]. Its full chemical name, oxalato(trans-L-1,2-diaminocyclohexane)platinum, refers to the presence of an oxalate "leaving group" and the DACH carrier ligand, which are responsible, at least in part, for its unique properties [2,3]. For example, unlike cisplatin, oxaliplatin in plasma rapidly undergoes non-enzymatic transformation into reactive compounds because of displacement of the oxalate group, a process that complicates its pharmacokinetic profile. Most of the compounds appear to be pharmacologically inactive, but dichloro(DACH) platinum complexes enter the cell, where they have cytotoxic properties.

3. MECHANISMS OF ACTION

Various mechanisms of action are ascribed to oxaliplatin. Like other platinum-based compounds, oxaliplatin exerts its cytotoxic effect mostly through DNA damage. Apoptosis of cancer cells can be caused by formation of DNA lesions, arrest of DNA synthesis,

inhibition of RNA synthesis, and triggering of immunologic reactions. Oxaliplatin also exhibits synergism with other cytotoxic drugs, but the underlying mechanisms of those effects are less well understood.

3.1 DNA Lesions

At intracellular physiological concentrations of HCO_3^- and $H_2PO_4^-$, and after aquation, dichloro(DACH)platinum compounds, once formed in plasma, enter the cell nucleus, where, with a peculiar tropism for GC-rich sites, they bind a nitrogen atom (N7) of guanine, forming DNA monoadducts, then diadducts [4]. Although the effect of oxaliplatin is mostly on genomic DNA, adducts are also formed in nucleosomes.

Oxaliplatin can induce 3 types of crosslinks:

- DNA intra-strand crosslinks
- DNA inter-strand crosslinks
- DNA–protein crosslinks

Intra-strand crosslinks seem to be the predominant mechanism of action in the induction of DNA lesions, with binding of two Gs [4], or less frequently, a G–A base pair.

Inter-strand crosslinks are believed to significantly contribute to the cytotoxicity of cisplatin [5], but seem less important in the mechanism of action of oxaliplatin. A study by Woynarowski *et al.* confirms both their presence at a low rate and their lethal properties [6].

As to DNA–protein crosslinks, despite their denaturating effect on enzymes and other important intracellular proteins, most studies have not proven that they cause cell death [5].

Monoadducts are devoid of significant cytotoxic action. Lethal DNA biadducts inhibit both DNA replication and transcription, causing apoptosis after cell cycle arrest [7] unless nucleotide excision repair has occurred. Formation of these DNA adducts is greater and more rapid with cisplatin than with oxaliplatin. Yet, oxaliplatin is, overall, more cytotoxic than cisplatin. The therapeutic effects of oxaliplatin therefore clearly do not depend only on the alkylating–intercalating effects of the platinum moiety [7].

The apoptotic pathway of colon cancer cells after exposure to oxaliplatin involves caspase 3 activation, translocation of Bax in the mitochondria, and release of cytochrome C in the cytosol [8].

Some aspects of the DNA lesions are relatively specific to oxaliplatin. For example, the conformation of oxaliplatin adducts, as compared with those of cisplatin or carboplatin adducts, makes binding with the mismatch repair (MMR) protein complex more difficult, presumably resulting in greater irreversibility of the lesions. In addition, the bulky DACH compound is postulated to more effectively prevent DNA synthesis than does the *cis*-diamine carrier ligand of cisplatin [2].

3.2 Arrest of DNA Synthesis

Experiments looking at the mechanism of synergism between oxaliplatin and 5-fluorouracil (5FU) have uncovered a direct inhibitory effect of oxaliplatin on thymidylate synthase, preventing the incorporation of thymidine in nucleic acid synthesis [9]. This antimetabolite-like effect results in arrest of the mitotic process. Because oxaliplatin is usually combined with 5FU, itself a thymidylate synthase inhibitor, it is unclear whether this mechanism of action of oxaliplatin plays an important role *in vivo* of its own.

3.3 Inhibition of Messenger RNA Synthesis

Inhibition of DNA replication is not always sufficient to cause cell death. Inhibition of transcription at the initiation and elongation phases also plays a key role. Three main mechanisms of transcription inhibition are postulated for oxaliplatin [10]:

- ***Binding of transcription factors:*** At the initiation stage, platinum–DNA adducts can serve as binding sites for transcription factors, especially when those factors have a strong chemical affinity for platinum. Thus, natural binding of the transcription factors to their promoter sites is prevented.
- ***Inhibition of RNA polymerases:*** This inhibition is established for cisplatin, but is presumably also true of oxaliplatin. The bases of platinum–DNA adducts are not able to enter the active site of an enzyme such as pol II.
- ***Role of nucleosomal DNA adducts:*** These adducts have the potential to block access by the RNA polymerase to the DNA template.

3.4 Immunologic Mechanisms

It has recently been discovered that oxaliplatin can cause the immunogenic death of colon cancer cells in murine and human cell lines [11]. After exposure to oxaliplatin, colon cancer cells emit several immunogenic signals on their surface before undergoing apoptosis. These signals trigger the production of interferon γ by T cells and also interact with the toll-like receptor 4 of dendritic cells, the whole process resulting in a sort of tumour vaccine. A particularly convincing argument of the importance of this mechanism is that humans carrying a mutant allele of the *TLR4* gene resulting in loss of function were found to experience a lesser benefit from oxaliplatin chemotherapy in the metastatic setting, with a statistically significant shorter progression-free and overall survival.

3.5 Mechanism of Action in Oxaliplatin-Based Combinations

Because single-agent oxaliplatin has low activity in many tumours, it is often combined with other chemotherapeutic agents, 5FU being the most common.

The exact mechanism of synergism between 5FU and oxaliplatin is complex, but experimental observations suggest that oxaliplatin can downregulate or inhibit dihydropyrimidine dehydrogenase, slowing the catabolism of 5FU [9].

Oxaliplatin has been combined with other cytotoxic therapeutic agents with varying degrees of success. The mechanism of action of these combinations is less well documented and beyond the scope of this article.

Relatively few data document the potential for synergism of oxaliplatin-based combinations with molecularly targeted therapy. *In vitro* experiments show enhanced cytotoxicity to cisplatin in cells pretreated with rapamycin, after suppression of DNA repair mechanisms by the latter agent [12]. Combinations of oxaliplatin with inhibitors of the mammalian target of rapamycin should be evaluated in the clinical setting.

3.6 Resistance to Oxaliplatin

Despite initial sensitivity to oxaliplatin, most cancer cells will eventually develop resistance. Many mechanisms of resistance have been described or hypothesized because of similarity between oxaliplatin and cisplatin [13,14]. The intracellular fate of the drug can be affected by decreased uptake (resulting in lower intracellular concentration) or inactivation by structural or spatial changes (conjugation with glutathione or sequestration with metallothionein). However, the most important mechanisms seem to be related to DNA repair: MMR, or nucleotide excision repair (NER). Cells that overexpress ERCC1, an excision repair enzyme, are resistant to oxaliplatin [15].

The combination of oxaliplatin with other antineoplastic drugs may prevent resistance—or even reverse it. For instance, *in vitro* assays show that cetuximab reduces the expression of components of NER pathways, used by the cell to remove platinum–DNA adducts [16]. A potential area of research would be the combination of oxaliplatin with inhibitors of Aurora kinases and of poly–adenosine diphosphate ribose polymerase [17].

3.7 Drug Interactions

Recent data show that oxaliplatin has little to no effect on cytochrome P450, one of the main enzymes involved in drug biotransformation [18]. That finding suggests that, when necessary, oxaliplatin may be safe to use in co-administration with other commonly used drugs.

4. TOXICITY PROFILE

Oxaliplatin causes adverse reactions that narrow its therapeutic index. The target organs are mainly the hematopoietic system, the peripheral nerves, and the gastrointestinal (GI) system.

4.1 The Hematopoietic System

Oxaliplatin is moderately myelotoxic, more so than cisplatin. The severity of myelotoxicity is proportional to the dose, typically 85–135 mg/m^2 intravenously. Grades 3 and 4 neutropenia are common, but with only a 4% incidence of neutropenic fever [19]. Anemia and thrombocytopenia are usually not severe.

Like many other cytotoxic drugs, oxaliplatin presumably affects progenitor cells in the bone marrow. It also enters peripheral blood cells: DNA adducts are present in leukocytes after oxaliplatin administration [20]. Whether this action contributes to hematologic toxicity is uncertain, but the number of platinum–DNA adducts in the blood cells of patients treated with cisplatin correlates with the degree of leucopenia and thrombocytopenia [21].

Other, less frequent, mechanisms of hematologic toxicity have been described. For instance, hypersensitivity reactions after repeated infusions of oxaliplatin can cause hemolytic anemia and secondary immune thrombocytopenia [22]. In addition, rare cases of secondary acute leukemia have also been reported, as with other alkylating agents [23].

4.2 The Peripheral Nerves

Peripheral neuropathy is extremely common in oxaliplatin-treated subjects. It exists in an acute and a chronic form, believed to result from distinct, but overlapping, pathophysiologic mechanisms.

Acute peripheral neuropathy is characterized by paresthesia, dysesthesia, or allodynia affecting the extremities, the lips, and the oropharyngolaryngeal area during or shortly after oxaliplatin infusion. It is often triggered by exposure to cold. It usually subsides within a few hours or days [24]. Experimental data suggest that oxaliplatin affects voltage-gated sodium channels in complex pathways involving calcium. Calcium itself is chelated by oxalate, a metabolite of oxaliplatin [25].

Chronic oxaliplatin-induced peripheral neuropathy results from cumulative exposure to the drug. The incidence of grades 3 and 4 neuropathy is about 15% [26] in patients who have received a cumulative dose of about 800 mg/m^2. It essentially involves the extremities. Although described initially as a degenerative process of the axons, in which the previously mentioned sodium ion channels play a role, it is now thought as well to be a state secondary to accumulation of platinum compounds in the dorsal root ganglia cells, causing atrophy and mitochondrial

dysfunction [27]. It is irreversible in fewer than 5% of cases. Most of the time, peripheral neuropathy manifests itself as decreased distal sensations and proprioception. As with the acute form, involvement of motor fibres is rare.

An understanding of the mechanism of peripheral neuropathy induced by oxaliplatin is crucial for the prevention and treatment of this phenomenon [28,29]. Many drugs for that purpose (for example, xaliproden, gabapentin) have been unsuccessfully tested. However, despite a previous controversy, the results of a retrospective study [30] and of an incompletely accrued randomized controlled trial [31] indicate a benefit with infusions of calcium gluconate and magnesium sulphate before and after oxaliplatin administration. The benefit consists of a significant reduction in the incidence of chronic peripheral neuropathy symptoms secondary to oxaliplatin. Although initially described, the improvement of acute neurotoxicity by this intervention has not been confirmed. There is no evidence to suggest a decrease in the anticancer effects of oxaliplatin when calcium and magnesium infusions are administered.

An additional research question is whether oxaliplatin can safely be combined with anti-neoplastics that have a different mechanism of neurotoxicity. Few studies in that regard have been performed, but uncontrolled trials suggest no increase in the incidence of severe peripheral neuropathy when oxaliplatin is associated with vinca alkaloids [32], taxanes [33], and proteasome inhibitors [34].

4.3 The GI System

The GI side effects attributed to oxaliplatin consist mainly of nausea, vomiting, and diarrhea [35]. Usually mild to moderate in intensity, they are considered to be nonspecific toxic effects of the drug on the rapidly dividing cells of the GI tract.

5. PHARMACOKINETICS

5.1 Generalities

Oxaliplatin is often administered concomitantly with 5FU. Phase I trials have shown no alteration of oxaliplatin pharmacokinetics when 5FU is administered concomitantly [36]. In addition, most papers do not address the pharmacokinetics of oxaliplatin *per se*, but of the platinum content. In fact, shortly after infusion, oxaliplatin forms many different platinum compounds that bind to blood or cell proteins. These molecules are thought to be of no pharmacologic interest [37]. Therefore, in most experiments, only the ultrafilterable platinum component is measured, which complicates interpretation of the pharmacologic data. Platinum derived from oxaliplatin is described as having a "tri-exponential" pattern of elimination, the half-lives being successively 0.28 hour, 16.3 hours, and 273 hours.

One paper reported the pharmacokinetics of oxaliplatin itself rather than of platinum after oxaliplatin infusion [38]. The half-life ($t_{1/2}$) of oxaliplatin is 14.1 minutes. Another half-life of 45 minutes is related to *in vivo* degradation in blood rather than to elimination. Also, "a significant correlation between the clearance and the *in vivo* degradation rate constants" was found, suggesting that there could be a physiologic link between those two processes.

5.2 Impaired Kidney Function

In a study examining the pharmacokinetics of oxaliplatin in the setting of renal function impairment [39], 34 patients were stratified according to creatinine clearance and received oxaliplatin at various dose levels.

The area under the curve (AUC) increased with lower creatinine clearance, supporting the understanding that the clearance of oxaliplatin occurs largely through renal mechanisms. However, no increased toxicity was observed, even with an increased AUC secondary to renal dysfunction.

5.3 Impaired Liver Function

Similarly, 60 cancer patients with liver dysfunction were stratified according to the results of liver function tests (total bilirubin, aspartate aminotransferase, and alkaline phosphatase) or their status as liver transplant recipients [40]. They received oxaliplatin 60–130 mg/m^2 according to a dose-escalation protocol.

Unlike renal insufficiency, liver dysfunction does not seem to affect oxaliplatin clearance and AUC, except in the group with the most severe abnormalities. No increased side effects were seen in the patients tested.

5.4 Long-Term Retention of Oxaliplatin Derivatives

Given that the 3rd half-life of oxaliplatin is in the order of hundreds of hours, accumulation of the drug in tissues may presumably be expected. In this regard, a study examined long-term retention of platinum 8–75 months after treatment with cisplatin and oxaliplatin [41].

The results showed that the plasma concentration of platinum in individuals previously exposed to oxaliplatin or cisplatin is larger by a factor of 30 than that in unexposed controls. The metal is found in both whole and ultrafilterable plasma. Risk factors for persistent high levels are decreased glomerular function and high cumulative dose. The authors demonstrated that the platinum found is still reactive, capable of forming platinum–DNA adducts *in vitro*. Although the physiologic significance of this reactivity is unknown, the findings are of concern with regard to long-term toxic effects such as secondary malignancies.

6. CLINICAL DEVELOPMENT OF OXALIPLATIN

6.1 Early Studies

The development of oxaliplatin was born of the need to find an alternative to cisplatin, an effective agent in various cancers, but substantially toxic. A recognized limitation of cisplatin was also its lack of activity against colorectal cancer, one of the most common human malignancies.

The phase I studies evaluated activity and safety for a range of doses. Unlike the usual classical studies, in which patient cohorts are given progressively higher doses of the studied drug, Mathé *et al.* used a different design: Doses were escalated in each study patient until the maximally efficient dose range, defined as between 45 mg/m^2 and 67 mg/m^2 administered intravenously, was reached [42]. An absence of nephrotoxicity, setting oxaliplatin apart from cisplatin, was observed. Hints of activity against lung cancer, breast cancer, melanoma, and hepatoma were noted.

In a more conventional phase I trial [43], dose escalation reached 200 mg/m^2 delivered intravenously. At that dose level, the characteristic peripheral neuropathy was recognized, leading to the recommendation, now accepted, that the maximum dose to be used in clinic be 135 mg/m^2 administered intravenously. Activity was also seen in various tumours, including some that had been pretreated with cisplatin.

Pharmacokinetic studies in that early period were also conducted. Although synergism between oxaliplatin and 5FU was rapidly recognized, relatively few pharmacodynamic studies were performed, possibly because of an assumption that oxaliplatin and cisplatin shared the same mechanism of action. However, interest in unmasking specific aspects of oxaliplatin arose when it was discovered that oxaliplatin and cisplatin are not cross-resistant.

6.2 Oxaliplatin in Colorectal Cancer

The modest activity (10%) of single-agent oxaliplatin in 5FU-refractory colorectal cancer was recognized early [44]. This activity rate is about 20% in untreated cases, according to a paper published in 1998 [45]. In both articles, the authors concluded that oxaliplatin combinations should be explored to improve outcomes. In fact, an uncontrolled study had already suggested synergy of 5FU and oxaliplatin, with reported response rates as high as 58% in a heterogeneous cohort of untreated and previously treated colorectal cancer patients [46].

The high activity of 5FU–leucovorin–oxaliplatin in 5FU-refractory colorectal carcinoma was confirmed in later trials, and the combination was given the acronym FOLFOX [47]. Several versions of this regimen have been developed (from FOLFOX1 to FOLFOX7) to improve 5FU-related toxicity and patient convenience. There is no strong evidence that any of the FOLFOX variations is superior to the others in terms of efficacy.

The real value of oxaliplatin in metastatic colorectal cancer has been demonstrated in randomized trials. For example, a phase III study conducted by de Gramont [48] comparing 5FU–leucovorin with FOLFOX4 in previously untreated metastatic colorectal cancer, showed a significant improvement in response rate (50.7% vs. 22.3%) and progression-free survival (9 months vs. 6.2 months) in favour of FOLFOX. Similar results have been reported in trials in which capecitabine was substituted for 5FU and leucovorin, forming the XELOX or CAPOX regimen [49]. In addition, oxaliplatin in combination with fluoropyrimidines remains useful, even after progression on 5FU–irinotecan, another standard regimen for metastatic colorectal cancer [50].

Given the effectiveness of oxaliplatin-based chemotherapy in advanced colorectal carcinoma, there was obvious interest for studies in the adjuvant setting. In patients who have undergone surgery for stage III colon cancer, 5FU or capecitabine (compared with observation) significantly improves the cure rate. Those results are furthered by the addition of oxaliplatin to the 5FU backbone. A recent publication confirms that, as compared with 5FU, FOLFOX improves overall survival in stage III patients [51].

Molecularly targeted cancer therapy is also added to oxaliplatin-based chemotherapy for the purpose of synergism. For now, the agents that are routinely used in that context are monoclonal antibodies. Clinical trials of bevacizumab, the antibody against vascular endothelial growth factor, in combination with FOLFOX or XELOX for metastatic colorectal cancer have shown positive results in terms of response rate, progression-free survival, or overall survival, depending on the particular clinical setting [52,53]. Improved response rates and progression-free survival are seen when an antibody (cetuximab or panitumumab) against the epidermal growth factor receptor (EGFR) is added to FOLFOX or XELOX, although the benefit of those antibodies is limited to patients harbouring an unmutated *KRAS* gene in their colorectal tumour [54,55].

Disappointingly, adding both bevacizumab and an anti-EGFR antibody to FOLFOX or XELOX is ineffective and even deleterious [56]. In addition, neither bevacizumab nor cetuximab improves overall survival or disease-free survival when given in combination with oxaliplatin-based chemotherapy in the adjuvant setting [57,58]. Overall, these results show how little is understood about the interaction of oxaliplatin with antibodies, and how useful pharmacodynamic studies would be in that regard.

Even fewer data are available regarding potential combinations of oxaliplatin with anti-angiogenic small molecules and multikinase inhibitors. The occasional antagonistic effects encountered in some *in vitro* experiments [59] highlight the need for careful research.

6.3 Other Cancers

Given its success in colorectal cancer, oxaliplatin has been tested in other digestive cancers. Because of its less toxic profile, many research protocols substitute it for cisplatin. The present review considers only gastroesophageal and pancreatic cancers.

In a phase III trial, Cunningham *et al.* [60] randomized patients with advanced gastric or esophageal cancer to either epirubicin–cisplatin–5FU or epirubicin–oxaliplatin–capecitabine. Response rate and progression-free survival were similar in both groups, suggesting equivalency between cisplatin and oxaliplatin, and between 5FU and capecitabine respectively.

Oxaliplatin in combination with 5FU or gemcitabine shows promising results as a salvage regimen for metastatic pancreatic cancer after failure of gemcitabine [61], but no results of phase III trials have yet been published in definitive form.

7. FUTURE PERSPECTIVES

Although it belongs to the same class of drugs as cisplatin and carboplatin, oxaliplatin shows marked differences in its pharmacokinetic and pharmacodynamic profiles, as well as in its spectrum of antitumour activity and its toxicity.

The pharmacology of oxaliplatin has uncovered one of the most appealing characteristics of the drug: its lack of cross-resistance with cisplatin and carboplatin, which complements its manageable toxicity profile. Pharmacodynamic characterization of oxaliplatin has also helped in achieving an understanding of the pathogenesis of the accompanying peripheral neuropathy, which should result in more effective management of that complication.

The discovery of multiple mechanisms of action of oxaliplatin, coupled with increased knowledge of cellular mechanisms of resistance, should facilitate design of clinical trials with novel combinations. An obvious goal would be to improve the results of current chemotherapy regimens without excessive toxicity. In particular, future studies should focus on combinations of oxaliplatin with molecularly targeted agents, because those combinations present potential therapeutic complementarity, with little overlap in pharmacologic characteristics.

8. CONFLICT OF INTEREST DISCLOSURES

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Importance of sequence in chemotherapy administration

Is sequencing important when administering chemotherapy on the same day? —Kathy Kerley, RN, OCN

Importance of sequence in chemotherapy administration

I think the best or correct order for drug administration is very difficult to answer. Administering chemotherapy apart from neutrophil growth factors is well known, and unless desired as a radiation sensitizer, avoid the use of chemotherapy during radiation. But the sequence of various chemotherapy drugs in general does not matter, as the half life of each drug will make it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics.

However, there are certain principles one can follow. For example, when administering a taxane in combination with a platinum, the taxane should always be given first. This is because myelosuppression has been observed in patients who received the platinum before the taxane. In published reports on various chemotherapy regimens, the original research articles may state the order in which the agents were administered, but this is rare. So basically, do not worry about order of chemotherapy drugs. —Donald R. Fleming, MD

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Art Unit	1612
Examiner Name	RONEY, Celeste A
Attorney Docket Number	01208-0007-01US

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/CELESTE A RONEY/ 09/02/2018

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15809815
	Filing Date	2017-11-10
	First Named Inventor	Bayever
	Art Unit	1612
	Examiner Name	RONEY, Celeste A
	Attorney Docket Number	01208-0007-01US

	1	OXALIPLATIN label, revised November 2013.
	2	CAMPTOSAR label, revised December 2014.

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EXAMINER SIGNATURE

Examiner Signature	/CELESTE A RONEY/	Date Considered	09/02/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Examiner Name	RONEY, Celeste A
Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2018-08-06
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

/CELESTE A RONEY/ 09/03/2018

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

/CELESTE A RONEY/ 09/02/2018

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

To: eofficeaction@appcoll.com,patents.us@ipsen.com,docketing@mcneillbaur.com
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Cc: PAIR_eOfficeAction@uspto.gov
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Sep 11, 2018 03:38:05 AM

Dear PAIR Customer:

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 153749 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15809815	CTFR	09/11/2018	263266-421428
	892	09/11/2018	263266-421428
	1449	09/11/2018	263266-421428

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Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15/809,815	Filing Date	2017-11-10	Docket Number (if applicable)	01208-0007-01US	Art Unit	1612
First Named Inventor	Eliel Bayever			Examiner Name	Celeste A. RONEY		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☒ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months 3
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 506488

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

X Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2019-02-11
Name	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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Privacy Act Statement

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Inventors: Eliel BAYEVER, et al. Application No.: 15/809,815 Filed: November 10, 2017 Title: METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	Group Art Unit: 1629 Examiner: Celeste A. RONEY Confirmation No.: 5137

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

VIA EFS WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicant brings to the attention of the Examiner the documents listed on the enclosed PTO/SB/08s. This Information Disclosure Statement is being filed with a Request for Continued Examination.

A copy of Mathé G, et al., "A Phase I Trial of Trans-1-diamino-cyclohexane Oxalate-platinum (I-OHP)," Biomed Pharmacother, 40:372-376 (1986) and Extra J, et al., "Phase I Study of Oxaliplatin in Patients with Advanced Cancer," Cancer Chemother Pharmacol. 25(4):299-303 (1990) are enclosed. The remainder of the listed foreign patent documents and non-patent literature documents are of record in parent application No. 15/241,106. Accordingly, copies of the latter documents are not enclosed.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

Applicant further reserves the right to take appropriate action to establish the patentability of the claimed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

McNeill Baur PLLC

Dated: February 11, 2019

By: /Mary R. Henninger, PhD/
Mary R. Henninger, PhD
Reg. No. 56,992
Telephone: 404-891-1400

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1629
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	1	6545010	B2	2003-04-08	Bissery	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2003013536	WO	A2	2003-02-20	Epidauros Biotechnologie AG		
	2	2011153010	WO	A1	2011-12-08	Abraxis Biosciences, LLC		

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	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Alberts S., et al. "Gemcitabine and Oxaliptatin for Metastatic Pancreatic Adenocarcinoma: A North Central Cancer Treatment Group Phase II Study," Ann Oncol. 14(4):580-5 (2003).	
	2	American Chemical Society (ACS), http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-what-is-pancreatic-cancer, retrieved December 1, 2016, 4 printed pages.	
	3	Assaf E, et al., "5-Fluorouracil/Leucovorin Combined with Irinotecan and Oxaliplatin (FOLFIRINOX) as Second-Line Chemotherapy in Patients with Metastatic Pancreatic Adenocarcinoma," Oncology. 80(5-6):301-6 (2011).	
	4	Azrak R, et al., "Therapeutic Synergy Between Irinotecan and 5-Fluorouracil against Human Tumor Xenografts," Clin Cancer Res. 10(3):1121-9 (2004).	
	5	Boeck S, et al., "Capecitabine Plus Oxaliplatin (CapOx) versus Capecitabine Plus Gemcitabine (CapGem) versus Gemcitabine Plus Oxaliplatin (mGemOx): Final Results of a Multicenter Randomized Phase II Trial in Advanced Pancreatic Cancer," Ann Oncol. 19(2):340-7 (2008), Epub 24 Oct 2007.	
	6	Burris H, et al., "Phase II Trial of Oral Rubitecan in Previously Treated Pancreatic Cancer Patients," Oncologist. 10 (3):183-90 (2005).	
	7	Cantore M, et al., "Combined Irinotecan and Oxaliplatin in Patients with Advanced Pre-Treated Pancreatic Cancer," Oncology 67(2):93-7 (2004).	
	8	Cereda S, et al., "XELIRI or FOLFIRI as Salvage Therapy in Advanced Pancreatic Cancer," Anticancer Res. 30 (11):4785-90 (2010).	
	9	Chang T, et al., "Phase I Study of Nanoliposomal Irinotecan (PEP02) in Advanced Solid Tumor Patients," Cancer Chemother Pharmacol. 75(3):579-86 (2015).	
	10	Chen L, et al., "Phase I Study of Liposome Encapsulated Irinotecan (PEP02) in Advanced Solid Tumor Patients," J Clin Oncol., 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition), 26(15S) (May 20 Suppl):2565 (2008), 1 page.	

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	11	Chen L, et al., "Phase I Study of Liposome Irinotecan (PEP02) in Combination with Weekly Infusion of 5-FU/LV in Advanced Solid Tumors," J Clin Oncol., 2010 ASCO Annual Meeting Abstracts, 28(15_suppl) (May 20 Suppl):e13024 (2010), 1 page.
	12	Chiesa M, et al., "A Pilot Phase II Study of Chemotherapy with Oxaliplatin, Folinic Acid, 5-Fluorouracil and Irinotecan in Metastatic Gastric Cancer," Tumori. 93(3):244-7 (2007).
	13	Conroy T, et al., "Irinotecan Plus Oxaliplatin and Leucovorin-Modulated Fluorouracil in Advanced Pancreatic Cancer-A Groupe Tumeurs Digestives of the Fédération Nationale des Centres de Lutte Contre le Cancer Study," J Clin Oncol. 23(6):1228-36 (2005).
	14	Delord J, et al., "Population Pharmacokinetics of Oxaliplatin," Cancer Chemother Pharmacol. 51(2):127-31 (2003), Epub 4 Dec 2002.
	15	Ducreax M, et al., "Randomized Phase II Study Evaluating Oxaliplatin Alone, Oxaliplatin Combined with Infusional 5-FU, and Infusional 5-FU Alone in Advanced Pancreatic Carcinoma Patients," Ann Oncol. 15(3): 467-73 (2004).
	16	ELOXATIN package insert, revision December 28, 2011, retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021492s012lbl.pdf, 51 pages.
	17	Fischel J, et al., "Ternary Combination of Irinotecan, Fluorouracil-Folinic Acid and Oxaliplatin: Results on Human Colon Cancer Cell Lines," Br J Cancer. 84(4):579-85 (2001).
	18	Gebbia V, et al., "Irinotecan Plus Bolus/Infusional 5-Fluorouracil and Leucovorin in Patients With Pretreated Advanced Pancreatic Carcinoma: A Multicenter Experience of the Gruppo Oncologico Italia Meridionale," Am J Clin Oncol. 33 (5):461-64 (2010).
	19	GLOBOCAN Cancer Facts Sheets: All Cancers 2012. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/all-new.asp, accessed on 3 Oct 2016, 9 printed pages.
	20	Goldstein D, et al., "nab-Paclitaxel Plus Gemcitabine for Metastatic Pancreatic Cancer: Long-Term Survival From a Phase III Trial," J Natl Cancer Inst. 107(2): dju413, pages 1-10 (2015).
	21	Grant S, et al., "Dose-Ranging Evaluation of the Substituted Benzamide Dazopride When Used as an Antiemetic in Patients Receiving Anticancer Chemotherapy," Cancer Chemother Pharmacol. 31(6):442-44 (1993).

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	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	22	Guichard S, et al., "Combination of Oxaliplatin and Irinotecan on Human Colon Cancer Cell Lines: Activity In Vitro and In Vivo," Anticancer Drugs. 12(9):741-51 (2001).	
	23	Hosein P, et al., "A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Adenocarcinoma," BMC Cancer. 12:199, pages 1-7 (2012).	
	24	Hoskins J, et al., "UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters," J Natl Cancer Inst. 99 (17):1290-95 (2007).	
	25	Jacobs A, et al., "A Randomized Phase III Study of Rubitecan (ORA) vs. Best Choice (BC) in 409 Patients with Refractory Pancreatic Cancer Report from a North-American Multi-Center Study," J Clin Oncol., 2004 ASCO Annual Meeting Proceedings 22(14S):4013 (2004).	
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Cancer Chemother Pharmacol (1990) 25: 299–303

Cancer Chemotherapy and Pharmacology

Phase I study of oxaliplatin in patients with advanced cancer

Jean Marc Extra[1], Marc Espie[1], Fabien Calvo[1], Christophe Ferme[2], Laurent Mignot[3], and Michel Marty[1]

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[3] Service d'Oncologie Médicale, Centre Médico-chirurgical Foch, 40 Rue Worth, F-92151 Suresnes, France

Summary. Oxaliplatin, or trans-1-diaminocyclohexane-platinum, was tested in a phase I study. A total of 44 patients received 116 courses with dose escalation from 45 to 200 mg/m^2. Neither renal nor hematologic toxicities were observed at doses up to 200 mg/m^2. Gastrointestinal toxicity was practically constant and often of grade 3–4 on the WHO scale (53% of patients). The dose-limiting toxicity was a peculiar sensory neuropathy; the first neurologic phenomena appeared at a dose of 135 mg/m^2 and continued thereafter, occurring after 75% of the courses with mild to moderate intensity (WHO grade 1–2 after 67% of the courses). Neurotoxicity was cumulative and six patients developed grade 3 disabling neuropathy after a cumulative dose of 500 mg/m^2, with walking and handwriting difficulties being slowly regressive in three cases. A peculiar symptom was the influence of temperature, with exacerbation of paresthesias when patients touched cold surfaces. Nerve-conduction studies carried out in six cases showed a predominantly sensory neuropathy with axonal degeneration. No other toxicities were observed, although audiograms were not systematically done. We observed four partial responses that lasted 6–13 months in patients with oesophageal (2 cases), lung (1), and urothelial cancer (1); two of these patients had been pretreated with cisplatin. Since neurologic side effects occur very frequently and may produce a long-lasting sensory neuropathy, for phase II studies we recommend a starting dose of 135 mg/m^2, with a careful neurologic survey.

Introduction

Cisplatin (CDDP) has demonstrated significant antitumor activity against animal and human malignancies. It is one of the best available cytotoxic drugs against testicular, ovarian, and head and neck cancers [1, 16, 26]. However, its use is limited by renal toxicity, severe nausea and vomiting, and, after large cumulative doses, occasional neurotoxicity.

With the aim of avoiding or reducing these deleterious side effects, numerous analogs of CDDP have been developed [3] and studied to obtain other active but less toxic compounds. Among them, carboplatin has reached phase III studies, demonstrating a similar antitumor activity in ovarian cancer [25]. Carboplatin produces moderate nausea and vomiting but no renal toxicity or ototoxicity; however, its major dose-limiting toxic effect is myelosuppression, and carboplatin doses have to be reduced when it is given with other myelotoxic agents.

Platinum complexes of diaminocyclohexane (DACH) isomers have been extensively studied in L1210 and P388 mouse leukemias, ascitic sarcoma 180, and murine solid tumors [9–11]. The trans-1 isomer called 1-OHP (trans-1-diaminocyclohexane platinum) appears to produce the maximal treated/control values in L1210 leukemia. A comparison of 1-OHP and CDDP [14] in these models gave similar results for the two compounds, but no nephrotoxicity was observed with 1-OHP as opposed to CDDP.

A phase I study was first conducted by Mathe et al. [15] in advanced cancer patients, with intrapatient dose escalation. The starting dose was $^1/_{10}$ of the maximally effective dose in mice, and a dose of 45 mg/m^2 was reached without limiting toxicity. Interestingly, four partial responses were observed among the 22 patients. To determine the maximal tolerated dose and dose-limiting toxicities, we undertook a new phase I study using a starting dose of 45 mg/m^2.

Patients and methods

To be eligible for this study, patients had to fulfill the following criteria: histologic proof of a malignant disease that had failed to respond to conventional chemotherapy or for which no such therapy existed, a minimal interval of 4 weeks since prior chemotherapy or radiotherapy, a minimal life expectancy of 8 weeks, and a WHO performance status of <4. All patients showed evidence of adequate bone marrow function (WBC count of $>3\times10^9$/l and platelet count of $>100\times10^9$/l), adequate liver function (bilirubin levels of <32 μmol/l), and adequate renal function (creatinine values of <200 mmol/l). All patients were informed of the investigational nature of this treatment.

Oxaliplatin was supplied by Roger Bellon laboratories in vials containing 10 and 100 mg. The drug was given by i.v. infusion in 0.9% NaCl, without pre- or post-hydration. The initial duration of perfusion was 1 h, which was prolonged to 6 h for doses of $>$ 135 mg/m^2 in cohort to

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Table 1. Diagnoses

Tumor type	Patients (*n*)
Lung cancer	11
Oesophageal cancer	7
Ovarian cancer	6
Adenocarcinoma of unknown primary	4
Soft-tissue sarcoma	4
Bladder cancer	3
Colon cancer	2
Cervix cancer	2
Breast cancer	1
Kidney cancer	1
Pleural mesothelioma	1
Teratoma	1
Vulvar cancer	1

Table 2. Dose-escalation scheme

Dose (mg/m^2)	Patients (*n*)	Courses (*n*)
45	3	5
60	2	7
90	3	5
135	14	39
150	14	28
175	7	22
200	5	10

Table 3. Gastrointestinal toxicity

Dose (mg/m^2)	Patients (*n*)	WHO grade:				
		0	1	2	3	4
≤90	8	0	2	2	3	1
135	12	0	2	2	8	0
150	11	1	2	3	4	1
175	7	1	2	1	2	1
200	5	0	1	0	3	1
Totals	43[a]	2	9	8	20	4

[a] One patient was nonevaluable

reduce gastrointestinal toxicity. The drug was given at 4-week intervals.

Antiemetics were not systematically given until the dose reached 90 mg/m^2, when gastrointestinal toxicity was universal.

A cohort of three patients was studied at the starting dose, and additional patients were entered at higher doses if no dose-limiting toxicity had occurred at the initial dose. Subsequent doses were chosen according to a modified Fibonacci scheme. There was no intrapatient escalation, but four patients received two different doses.

Serum tests were carried out on the day of therapy and weekly thereafter. These included determinations of sodium, potassium, chloride, creatinine, liver enzymes and bilirubin, WBC counts with differential counts, hemoglobin, and platelets. Monthly magnesium and phosphorus determinations as well as electrocardiograms and chest roentgenograms were carried out. Other investigations were done according to the individual patient's symptoms. Toxicities were evaluated according to WHO criteria.

Results

A total of 44 patients entered this phase I study and received 116 courses (median, 2; range, 1–6), including 28 men and 16 women with a median age of 57 years (range, 26–81 years). In all, 22 patients had a performance status of 2–3. The tumor types are described in Table 1.

Prior to this study, 38/44 subjects had received chemotherapy consisting of a median of four cytotoxic agents (range, 1–11), and 32 patients had received CDDP (median cumulative dose, 210 mg/m^2; range, 80–700 mg/m^2).

The number of patients and courses at each dose level is shown in Table 2. The cohort of subjects who received 150 and 135 mg/m^2 is important because of the limiting neurologic toxicity that appeared at these doses. No direct treatment-related death occurred in this study. All but two patients experienced nausea and vomiting, which occurred at the lower doses (Table 3). The severity of vomiting did not appear to be dose-related, and grade 3–4 emesis was noted in 24/43 cases; however, it was of short duration. Diarrhea occurred less frequently (24% of courses) and was less severe (90%, grade 1–2). Gastrointestinal toxicity was not influenced by the duration of the infusion (1 h vs 6 h).

Hematologic toxic effects secondary to oxaliplatin treatment are shown in Table 4. No severe (grade 3–4) leukopenia was observed, the nadir being 2.6×10^9 cells/l.

Table 4. Hematologic toxicity

Dose (mg/m^2)	WBC nadir ($\times 10^9$/l):		Platelet nadir ($\times 10^9$/l):		Hemoglobin nadir (g/l):	
	Median	Range	Median	Range	Median	Range
≤90	10	3.9–17.6	277	160–360	94	70–120
135	5.9	3.4–9.7	181	50–338	101	85–120
150	4.7	2.6–7.2	140	16–221	105	80–130
175	4.2	3.0–5.5	114	63–175	107	90–126
200	4.7	2.6–6.3	124	75–220	86	77–100

Table 5. Incidence of neurologic side effects during the first course

Dose (mg/m^2)	Patients (n)	Patients with neurologic side effects:	
		(n)	(%)
135	14	7	(50%)
150	14	9	(64%)
175	7	5	(71%)
200	5	5	(100%)

Table 6. Intensity of neurotoxicity

Dose (mg/m^2)	Evaluable courses (n)	Courses with neurotoxicity (WHO grade):			
		0	1	2	3
135	39	15	19	4	1
150	28	6	14	5	3
175	22	3	12	5	2
200	10	1	6	2	1
Totals	99	25	51	16	7

Table 7. Influence of cumulative dose on neurotoxicity

Cumulative dose (mg/m^2)	Patients (n)	Patients with neurotoxicity (WHO grade):			
		0	1	2	3
<270	21	14	5	1	1
270–540	11	3	7	2	0
>540	9	0	3	1	5

Mild to moderate thrombocytopenia (grade 1–2) was observed in 14/90 evaluable courses. One severe case of thrombopenia (10×10^9 platelets/l) was observed in a women who had previously developed grade 4 thrombocytopenia after each course of CDDP. Thrombocytopenia was dose-related; it did not occur in any of the patients treated with 45–90 mg/m^2 but was seen in 13% of patients receiving 135–150 mg/m^2 and in 28.5% of those treated with 175–200 mg/m^2. No significant renal toxicity was observed. Four cases of grade 1 and one case of grade 2 renal toxicity were rapidly reversible. However, sequential creatinine clearance measurements were not systematically carried out. No significative changes were observed for magnesium, calcium and other electrolytes.

The dose-limiting side effect was a peculiar neurotoxicity. Paresthesias of fingers, hands, toes and, sometimes, lips developed with a dose-related frequency. They were not observed below 90 mg/m^2 but occurred during the first course with an incidence of 50%, 64%, 71%, and 100% at doses of 135, 150, 175, and 200 mg/m^2, respectively (Table 5). These side effects occurred in 75% of courses at doses of >90 mg/m^2, and their intensity was generally mild (51% of courses) to moderate (16%) according to WHO criteria (Table 6).

Clinically, paresthesia appeared during 1-OHP infusion, and the duration of symptoms was brief (<1 week) after the first course but tended to be longer with subsequent courses. Sensory neuropathy developed after subsequent courses, with increasing intensity (grade 3 toxicity was noted after the fourth course in 5/6 patients), with increasing duration (symptoms were permanent after the fourth course in 63% of cases vs 10% before this course). In these cases dysesthesias involved the extremities as well as the forearms, legs, mouth, and throat. Six patients developed grade 3 neurotoxicity, one of whom had a very transient laryngospasm at two consecutive courses, and five after the fourth course. Four of the latter developed marked ataxia, with difficulty in walking.

This neuropathy has slowly regressed with symptoms disappearing after 6 months. Table 7 shows the relationship between the cumulative dose and the severity of neurotoxicity.

When carried out (in six cases), electromyograms showed an axonal sensory neuropathy. No significant changes in motor nerve-conduction velocities were noted.

Table 8. Characteristics of eigth patients with a partial response or stable disease

Tumor type	Dose (mg/m^2)	Courses (n)	Response[a] (duration in months)	Prior response to CDDP[b]
Urothelial	60	5	PR (6)	NE
Oesophageal	135	5	PR (6)	+
Lung	135	6	PR (10)	NE
Oesophageal	175	6	PR (13)	–
Cervical	150	3		
	175	3	SD	+
Pleural mesothelioma	175	6	SD	NE
Teratoma	150	6	SD	+
Chondrosarcoma	175	5	SD	–

[a] PR, partial response; SD, stable disease

[b] NE, no prior exposure to CDDP; +, patients responding to CDDP; –, patients whose disease progressed during CDDP therapy

There was no clear correlation between these neurologic side effects and previous exposure to CDDP or vinca alkaloids: 59% and 42% of patients with and without prior CDDP treatment, respectively, developed neurologic side effects after receiving 1-OHP. The median cumulative doses of CDDP and 1-OHP were 270 and 845 mg/m^2, respectively, for subjects with grade 2–3 neurotoxicity, 330 and 400 mg/m^2 for those with grade 1 neurotoxicity, and 90 and 175 mg/m^2 for patients without neurologic side effects. Neither central nervous system toxicity nor ototoxicity was observed, although audiograms were not systematically done.

Other toxicities included phlebitis (one case), mild fever (three cases), and transient and mild increases in liver enzymes (six cases). Neither cardiac toxicity nor alopecia was observed in the evaluable patients.

Objective responses were observed in four subjects, with partial responses of 6–13 months' duration. Four other patients had a stabilisation of their disease, with no progression occurring for >6 months.

Of these eight patients, five had previously been treated with CDDP, two of them showing disease progression under this drug (Table 8). The first of these two patients had oesophageal cancer that had progressed on therapy consisting of CDDP, fluorouracil, and bleomycin, with the appearance of disease in the left supra-clavicular lymph node; this patient responded to 1-OHP and relapsed after 13 months. The second subject had developed progressive lung metastases of chondrosarcoma on therapy with CDDP, etoposide, and ifosfamide and experience a good stabilisation after 6 months of 1-OHP treatment. Interestingly, all partial responders had cancer of epithelial origin.

Discussion

Oxaliplatin, a new DACH-platinum analog, was evaluated in 44 patients at a dose range of 45–200 mg/m^2. Neither hematologic nor renal toxicities were dose-limiting. Gastrointestinal toxicity was practically constant and frequently severe (grade 3–4 in 24/43 cases) but not unequivocally dose-related.

The dose-limiting toxicity was neurologic, with a peculiar sensory neuropathy occurring first at a dose of 135 mg/m^2 and very frequently at higher doses. Its onset was acute, cold-related, and mainly involved the extremities. Its duration and intensity were influenced by the cumulative dose, with three patients developing a disabling neuropathy that regressed slowly; these patients received a dose of >500 mg/m^2 1-OHP. Interestingly, these side effects were not influenced by prior exposure to CDDP.

Neurotoxicity is rarely dose-limiting with cytotoxic agents other than cisplatin, vinca alkaloids, and hexamethyl-melamine. Peripheral neuropathies have rather infrequently been identified with CDDP therapy, with an incidence range of 2.7% [24] to 4.3% [20]; however, these studies were retrospective, and recent, careful neurologic surveys [21] have noted a predominantly sensory peripheral neuropathy in 92% of patients receiving the compound. In the present study as well as others using CDDP [2, 7], the development of peripheral neuropathy appeared to be dose-related, with most patients receiving a cumulative dose of ⩾300 mg/m^2. With high-dose CDDP regimens (40 mg/m^2 daily ×5), disabling neurototoxicity has recently been noted, with an increased incidence ranging from 29% to 62.5% [4, 5, 12, 18, 19, 23]. Clinically, except for the effect of cold, 1-OHP-induced neuropathy mimicked that of CDDP, with predominantly sensory symptoms affecting the upper and lower extremities.

Paresthesias and dysesthesias are characteristic of this neuropathy; in severe cases, handwriting and walking difficulties are presumably related to proprioceptive abnormalities [7]. With both drugs, disabling neuropathy developed only after a high cumulative dose (300 mg/m^2 for CDDP, 500 mg/m^2 for 1-OHP); although all symptoms improved after the discontinuation of therapy, in some cases long-term deficits persisted. The main differences between 1-OHP- and CDDP-related neuropathy involve its acute onset at a dose of 135 mg/m^2 1-OHP and its temperature dependency, with exacerbation of symptoms after contact with cold surfaces or liquids.

Nerve-conduction studies and nerve biopsies have been carried out in CDDP-induced neuropathy, suggesting that the toxic mechanism involves segmental demyelinisation [2, 17] or axonal degeneration [6, 13]. Several authors [6, 8] have suggested that CDDP peripheral neuropathy might be similar to that of thallium salt toxicity. Others have suggested vitamin B12 inactivation, but this was not confirmed in a recent study [22]. More studies are needed to clarify the actual mechanisms of platinum-salt neurotoxicity. This neurotoxicity is a particularly prominent problem with oxaliplatin, but we noted that when symptoms (paresthesias) receded completely between two courses, there was no long-lasting sensory neuropathy. In contrast, when symptoms lasted until the subsequent course and the treatment was continued, severe sensory neuropathy was more likely to occur.

During this phase I study on 44 subjects, we observed four partial responses in patients with oesophageal (2), lung (1), and urothelial cancers (1). For future phase II studies, we recommend a starting dose of 135 mg/m^2 and a careful survey of neurologic side effects (nerve-conduction studies), particularly after a cumulative dose of 500 mg/m^2, when these side effects are constant and patients are at risk to develop long-lasting sensory neuropathy.

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A PHASE I TRIAL OF TRANS-1-DIAMINO-CYCLOHEXANE OXALATO-PLATINUM (l-OHP)

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ABSTRACT

Oxalato-platinum in a new platinum derivative which was found to be active in experimental tumors and devoid of nephrotoxicity. A phase I study was conducted in cancer patients according to a new design following the recommendations of our Institution's ethical committee to avoid the major drawback of classical phase I studies in which many patients receive the experimental drug at doses far under the potentially active dose extrapolated from experimental studies. The potentially active dose of l-OHP was determined from the Maximally Efficient Dose Range (MEDR) to be between 45 mg/m² (subcurative dose) and 67 mg/m² (subtoxic dose). The patients in this study received with increasing intervals 1/100, 1/10, 1/5, 1/3, 1/2, 2/3, 3/4, 1, of the low dose of the MEDR, this dose being reached after 90 to 120 days on study. 23 evaluable patients have entered the trial of which 19 reached the low dose of MEDR (45 mg/m²). Gastro-intestinal toxicity, nausea and vomiting, similar to those with CDDP occurred in all patients at or above the dose of 30 mg/m². Renal toxicity was monitored with creatinine level and did not occur in any patient at any dose nor did significant hematologic toxicity occur. Thus nausea and vomiting appear to be the limiting toxicity of the drug. Responses were observed in this phase I study in lung cancer (1), breast cancer (1), melanoma (1) and perhaps hepatoma (major decrease in αFP levels) (1). The proposed starting dose for phase II studies is 45 mg/m² but we plan to continue dose escalation during the phase II according to the design of Jones and Holland. This new study design allows each patient entering a phase I study to be treated with a potentially active dose of the drug studied.

ABRÉGÉ

L'oxatalo-platinum (l-OHP) est un nouveau dérivé du platine doué d'une forte activité antitumorale sur les modèles expérimentaux et dénué de néphrotoxicité. Nous avons réalisé un essai phase I chez des patients cancéreux en utilisant un nouveau modèle d'augmentation progressive des doses chez chaque malade, selon les recommandations de notre comité d'éthique, pour éviter que de nombreux malades ne reçoivent le médicament à des doses très inférieures aux doses potentiellement actives extrapolées de l'expérimentation animale. La dose potentiellement active à l-OHP a été déterminée à partir de l'intervalle de doses maximalement efficaces (MEDR) chez les souris, c'est-à-dire entre 45 mg/m² (dose subcurative) et 67 mg/m² (dose subtoxique). Les patients de notre étude ont reçu à des intervalles de temps croissants, 1/100, 1/10, 1/5, 1/3, 1/2, 2/3, 3/4, 1 de la dose basse du MEDR, cette dernière étant atteinte après 90 à 120 jours. 23 patients ont été inclus dans cette étude dont 19 ont atteint la dose basse du MEDR; la toxicité digestive, faite de nausées et de vomissements, semblable à celle du cis-diamino-dichloro-platinum a été observée chez tous les patients à partir de la dose de 30 mg/m². Il n'y a eu aucun cas d'insuffisance rénale et aucune toxicité hématologique significative. La toxicité digestive paraît être la toxicité limitante du médicament. Une efficacité antitumorale a été observée, dans un cas de cancer du poumon, dans un cas de cancer du sein, dans un cas de mélanome malin et dans un cas de carcinome hépatocellulaire. La dose basse du MEDR, 45 mg/m² est une dose sans danger et est proposée comme dose de départ de l'essai de phase II durant lequel nous prévoyons de continuer l'escalade des doses selon le modèle de Jones et Holland. Ce nouveau modèle d'essai de phase I permet à chaque patient inclus de recevoir des doses potentiellement actives du médicament étudié.

Cis-diamino-dichloro-platinum (CDDP) introduced by Rosenberg (1) in 1969, is a powerful cytostatic agent that is frequently and successfully used in clinical cancer chemotherapy (2). It has however significant side effects among which in the short term nausea and vomiting are the most feared, and in the long term renal toxicity, otovestibular toxicity and allergic reactions.

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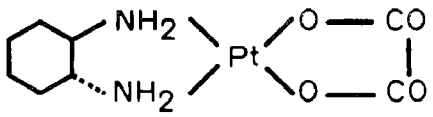
To try to avoid this toxicity, other Pt(II) complexes have been prepared, including the oxalato-Pt(II) complex of diamino-cyclohexane (DACH) obtained as isomeric mixtures, and which is active on several murine tumors (3-6).

Kidani *et al.* (7) succeeded in separating DACH into geometric isomers, cis and trans, and then separated the trans into 2 optical isomers: trans-d and trans-l. Among the complexes they prepared, the oxalato Pt(II) complex of the trans-l-DACH (Fig. 1) appeared to have the maximal T/C (treated/control) values on L1210 leukemia.



l-OHP

FIG. 1.

We have used l-OHP on our murine tumor screening system and found it more active than CDDP on L1210 leukemia. On AKR leukemia, l-OHP was as active as CDDP but less toxic. Moreover, in murine large cell lymphoma and L1210 grafted intracerebrally l'OHP increased the life span while CDDP was inactive (7).

As compared to CDDP on the basis of toxicity, the tolerance superiority of l-OHP was remarkable over the latter. The absence of nephro-toxicity was histologically confirmed in mice and also observed in baboons.

We present in this paper the preliminary results of a phase I clinical trial of l-OHP employing a new method of intra-patient escalation conducted from June 84 in the « Service des Maladies Sanguines et Tumorales ».

PATIENTS AND METHODS

Twenty-three patients with histologically confirmed malignancy were evaluated in this study. Most patients had exhausted all standard therapy and in the two patients with no previous treatment the disease was the one for which no therapy of proven benefit was available. All but one had never received cisplatin before (Table I).

Patients were asked for informed consent and on entry all had a performance status of at least 50 % (on Karnofsky scale) and a minimum of life expectancy of 2 months. All the pretreated patients have been off previous chemotherapy or irradiation for a period of 4 weeks.

Prior to beginning l-OHP treatment, patients were required to have an adequate renal function, WBC $> 4{,}000/mm^3$, platelet count $> 100{,}000/mm^3$ and Hb > 10 g/dl. Some liver dysfunctions were not considered as contra-indications in patients with hepato-carcinoma or those with confirmed hepatic metastases.

Baseline and follow up studies for tolerance included weekly evaluation of body-weight and surface, performance status, complete blood cells counts with differential, renal function: blood urea and creatinin, electrolytes, blood proteins, liver function tests and enzymes, electrocardiogram, and monthly chest X ray and tumor measurement if applicable including tumor markers such as CEA, alphafetoprotein, lipid-bound sialic acid, according to each particular case. Toxicity as well as anti-tumor activity were evaluated and graded according to W. H. O. criteria (8).

Patients characteristics and tumors are shown in Table I.

Drug and schedule of administration

L-OHP was kindly supplied by R. Bellon Laboratory, as a formulation in

1 ml vials containing 1 mg
10 ml vials containing 10 mg

and 100 ml vials containing 100 mg of 1,2-diamino-cyclohexane (trans-l) oxalato-platine II (Fig. 1).

TABLE I

Patients characteristics.

Number of patients evaluated		23
	Sex ratio male/female	14/9
	Age range in years	21-77
	Average	51
Prior therapy		
	None	2
	Chemotherapy only	12
	Chemotherapy and hormonotherapy	1
	Chemotherapy and immunotherapy	3 (*)
	Radiotherapy only	2
	Chemotherapy and radiotherapy	4
Previous CDDP		1
Tumors:	Unknown primary	2
	Breast cancer	3
	Intraocular melanoma	1
	Lung cancer	1
	Malignant melanoma	9
	Primary liver tumor	3
	Prostate cancer	1
	Cholangiocarcinoma	1
	Small bowel carcinoma	1
	Schwanoma	1

(*) 1 patient received chemotherapy, radiotherapy and immunotherapy.

The doses and schedule of administration of the drug were chosen according to the new ethical rules of phase I trials (9) with a dose escalation scheme in each patient so that every patient entering the trial would have a chance to benefit from the drug. The starting and escalation doses were determined from the MEDR (10) doses in mice (7) ranging from 45 mg/m^2 (subcurative dose) to 67 mg/m^2 (subtoxic dose).

Despite the low toxicity of l-OHP observed in animal models (namely in mice and baboons) we have chosen as the starting dose the 1/100 of the Maximally Efficient Dose Range in mice in order to detect any reaction of anaphylaxis or hypersensitivity of the patient to the drug. Because of the reported risk of nephrotoxicity for most derivatives of platine known up to date, prior to l-OHP administration patients were hydrated with 1 l of

IV fluids (containing 5 % dextrose in 0.4 % saline with 2 g KCl) and mannitol given as previously described. The use of antiemetics was not indicated for the first three dose levels.

Table II shows dosage escalation in each patient and the day of administration. The high dose of Maximally Efficient Dose Range (MEDR) is reached by day 120 of treatment if all intermediate doses are given. When all the doses of the schema have been given without adverse effects in the first patients, some intermediate doses may be omitted in the following ones to reach more quickly the potentially active dose supposed to be similar to MEDR in mice.

TABLE II

Dose escalation table.
Modality of Administration: IV infusion.

0.45	Day 1
4.5	Day 1 afternoon
9	4
15	11
22.5	3 weeks interval
30	
45	
56	
67	

RESULTS

Twenty-three patients were available for evaluation of toxicity during the period from June 84 to February 1986.

There was no treatment related death nor any disruption of the drug consecutive to unacceptable toxic effects during the study. No reaction of anaphylaxis or hypersensitivity to the drug was observed. 20 patients were treated at least at three dose levels namely 1/100-1/10 and the subcurative dose extrapolated from the MEDR (Maximally Efficient Dose Range) established in mice, that is 45 mg/m². The other 3 patients were withdrawn from protocol for early rapid disease progression. Eleven out of the 23 evaluated patients have reached the subtoxic dose level established in mice, that is 67 mg/m². Patients received from 3 to 14 cycles with an average of 7-8 cycles, Table IV indicates the number of patients having been treated at each dose level and the main toxic effects observed in this study.

The total dose range extended from 78 mg to 1,002 mg. The patient with 78 mg was accepted for evaluation for toxicity because was already treated at the three dose levels *i. e.* 1/100, 1/10 and 45 mg/m² with one cycle at each dose level, and by the moment of this writting this patient was still on study. The median total dose was approximately 500 mg.

Hematologic toxicity

Anemia was observed in three patients during this study but only one of these patients was assessable for hematologic toxicity evaluation. The other two patients are not considered evaluable for the following reasons:

1. one patient had a positive bone marrow biopsy.
2. the second patient presented anemia and mild thrombocytopenia grade I on WHO scale (Hb 9.7 g/dl and 124,000/mm³ platelets) only after six months of treatment at the same time the disease was progressive and for this reason l-OHP therapy was discontinued. It may be more likely to consider these symptoms as consecutive to progressive disease rather than due to toxicity. Unfortunately bone marrow biopsy was not performed in this patient. In the patient available for evaluation anemia appeared on day 40 of treatment, lasted approximately 4 weeks with stable value of Hb between 9.9 g/dl and 9.5 g/dl which is evaluated as grade I on WHO scale. Neutropenia was not observed in this patient and in none of the patients of this study.

Non-hematologic toxicity

Non-hematologic toxicity was confined to nausea and vomiting. Nephrotoxicity was not observed on the basis of increase of serum creatinine or by urea dosage. No alopecia was reported by any of the patients nor mucositis. Modification of liver enzymes was limited to one patient. Out of the 22 evaluated patients only one presented increase of serum alkaline phosphatase with absence of hepatic metastasis confirmed by hepatic echography and scanning. This disturbance of hepatic function consecutive to l-OHP treatment was transient and evaluated as grade I on WHO scale.

Although the use of antiemetics made it difficult to evaluate adequately this side effect, nausea and vomiting were first encountered at 30 mg/m² in one out of the 9 patients and by 45 mg/m² up, in all patients intered in this study. The intensity of the symptom was dose dependent but did not prevent the continuation of therapy although it might be a cause of considerable anxiety for the patient. The failure to continue l-OHP treatment in these evaluated patients was due to progressive disease rather than to limiting toxicity of any kind.

The preliminary results of this first clinical trial confirmed the encouraging data obtained from previous studies on animal models and provided additional evidence for the better tolerance to l-OHP than to other derivatives of platine and namely CDDP because of the absence of nephrotoxicity and the relative lack of myelosuppression which is in contrast with the significant hemotologic toxicity observed with other analogs of platinum such as Ipro-

TABLE III

Tolerance.

Dose level	No. patients N = 23	Toxicity							
		Nausea vomiting	Lung	Heart	Liver	Kidney	Hematopoiesis Hb	WBC	Platelet
0.45	21	—	—	—	—	—	—	—	—
4.5	21	—	—	—	—	—	—	—	—
9	9	—	—	—	—	—	—	—	—
15	12	—	—	—	—	—	—	—	—
22.5	8	—	—	—	—	—	—	—	—
30	9	1/9	—	—	—	—	—	—	—
45	19	19/19	—	—	—	—	1/19 Gr1	—	—
56	15	15/15	—	—	1/15	—	1/15 Gr1	—	—
67	11	11/11	—	—	—	—	1/11 Gr2	—	1/11 Gr1

Parameters evaluated:
Liver: transaminases, alkaline phosphatase.
Kidney: urea, creatinine.
Gr : grade according to WHO (8).

TABLE IV

Antitumor activity.

Response	No. patients	Tumor + target	Total dose received	Imaging
Progressive disease	16/23			
Stabilisation	3/23	1 prostate + liver and bone metastasis	798 mg	Echo + PAP
		2 liver	843 mg	
		3 liver	943 mg	αFP
Minor response	1/23	Lung	740 mg	Tomo-scan
Partial response	1/23	Breast carcinoma + bone metastasis	473 mg	Scintigraphy
Complete response	1/23	Melanoma + metastases of the lung and parotid	297 mg *	Scan (of the head and lung)

* *N. B.:* This patient is still on study. Although he has reached only a low level (45 mg/m²) at the time of this report the results as evidenced by scan of the and the head confirmed a complete disappearance of the metastases of the lung and the parotide seen before treatment.

platin or SHIP (11). The recommended starting doses for phase II trial will be 67 mg/m² but higher doses may be reached in a dose escalation phase II design, according to Norton's model (12). Toxicity results are presented in Table IV.

Response data

Evaluation of efficacy was not the principal aim of this first clinical trial but some very interesting and encouraging responses were observed.

Data are summarised in Table IV.

The preliminary results of the present paper demonstrate the good tolerance of l-OHP in man at the higher dose of the MEDR established in mice and suggests that subtantial antitumor activity of l-OHP might be obtained principally in hepatocarcinoma and colorectal carcinoma. Nevertheless these encouraging data must be confirmed by further phase II clinical study.

CONCLUSION

In conclusion we confirm the safety of l'OHP at the dose extrapolated from the MEDR in mice, dose at which antitumor responses have been observed. The fact that we did not reach a dose limiting toxicity is inherent to the new design of this phase I study, the objective of which was to confirm the tolerance of the high dose of MEDR. Further dose escalations are planned within the phase II study according to the Norton's model.

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Biomedicine & Pharmacotherapy, 1986, *40*, 376-379.

AN ORIENTED PHASE II TRIAL OF THP-ADRIAMYCIN IN BREAST CARCINOMA

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ABSTRACT

THP-ADM is a new anthracyclin with broad antitumor activity without cardiac toxicity or alopecia in experimental models. Phase I studies had established a proposed dose for phase II trials of 50 mg/m² every three weeks. This modality gave an insignificant result in breast carcinoma. Cellular pharmacokinetics suggested that a longer time of administration could be more efficient. In this phase II trial oriented to advanced breast cancer, we have used 3 consecutive daily doses of 20 mg/m²/day in monthly cycles with dose escalation in each patient. We have observed 28 % partial remissions (PR). Two patients previously treated with adriamycin had PR. Significantly less alopecia and no cardiac toxicity were observed.

ABRÉGÉ

La tétrahydropyranyl adriamycine, THP-ADM est une nouvelle anthracycline dotée d'une large activité antitumorale et dépourvue de cardiotoxicité sur les modèles expérimentaux. Les études de phase I avaient établi une dose initiale de 50 mg/m² chaque trois semaines pour les essais de phase II. Cette modalité n'a pas donné de résultats appréciables dans le cancer du sein. Les résultats de la pharmacocinétique cellulaire du médicament ont suggéré qu'une administration plus prolongée pourrait être plus efficace. Dans l'essai phase II présenté ci-dessous dans les cancers du sein, nous avons administré trois doses quotidiennes consécutives de 20 mg/m² chaque mois avec escalade des doses chez un même malade. Nous avons observé 9 réponses partielles (28 %). Deux patients ayant préalablement reçu de l'Adriamycine à titre adjuvant ont obtenu une rémission partielle. Nous n'avons pas observé de toxicité cardiaque et une alopécie significativement moindre qu'avec l'Adriamycine.

Adriamycin (ADM) is one of the most efficient agents to induce complete and partial remissions (CR and PR) in advanced breast carcinoma (2). It induced CR + PR in 36 out of 121 patients (30 %) according to Blum and Carter (1). Toxicity of anthracyclins affecting the hair and heart (4, 5) are however stumbling blocks to some uses (2). Among all available anthracyclins that we studied experimentally for hair and cardiac toxicity (4, 5), (4'-0-tetra-hydropyranyl-adriamycin-hydrochloride) or THP-Adriamycin proved to be one of the two least toxic analogues while highly active on experimental tumors such as P388, L1210 and Lewis tumor (14).

Majima (8) concluded a phase I study by recommending, for phase II trials, to use THP-ADM in a

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Reprints: G. Mathé.

Electronic Patent Application Fee Transmittal

Application Number:	15809815
Filing Date:	10-Nov-2017
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Filer:	Mary Rucker Henninger/richard king
Attorney Docket Number:	263266-421428

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
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RCE- 1ST REQUEST	1801	1	1300	1300
		Total in USD ($)		**2040**

Electronic Acknowledgement Receipt

EFS ID:	35119993
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger
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Attorney Docket Number:	263266-421428
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1		2019-02-11_237IBL_P7_US-A_01208-0007-01US_Response_to_FOA_as_filed.pdf	301957 33a6bd5f0a0b82dc4114d3b281560022d3dfb29c	yes	17

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	6	17
Claims	2	5
Transmittal Letter	1	1

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2	Extension of Time	2019-02-11_237IBL_P7_US-A_01208-0007-01US_EOT.pdf	164607 2d16d62d63d03ae7d71c19b06af37ca0e65c5012	no	2

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3	Request for Continued Examination (RCE)	2019-02-11_237IBL_P7_US-A_01208-0007-01US_RCE.pdf	1364397 dbef5544b066dd1f01b4d1133f64ba90c31efb07	no	3

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4	Transmittal Letter	2019-02-11_01208-0007-01US_IDS_Transmittal.pdf	130784 b2d443203764 1f9f00e9f531fde014f29ff8b434	no	2

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

I. Status of Claims

Following entry of this amendment, claims 1, 4 to 15, 18, 19, 21 to 23 are pending in the application. Claims 2, 3, 16, 17, and 20 were previously canceled without prejudice or disclaimer. Applicant expressly reserves the right to pursue the subject matter of those claims in the future. Claims 1, 11, 19, 21, and 22 were amended to even more clearly recite the subject matter being claimed. Support for the amendments and new claim 23 can be found throughout the specification and originally filed claims, for example at original claim 18. The amendments and new claims add no new matter.

II. Rejections Under 35 U.S.C. § 103

Rejection of claims 1, 5-8, 10 and 19

Claims 1, 5-8, 10 and 19 are rejected under 35 U.S.C. 103 as allegedly being unpatentable over WO 2013/188586 ("Bayever"), in view of Conroy et al., N Engl J Med., 364(19):1816-25, 2011) ("Conroy"), and further in view of Alcindor et al., Curr Oncol, 18(1):18-25, 2011 ("Alcindor"). Office Action at p. 2. The Examiner asserted that Bayever discloses treatment of metastatic pancreatic cancer comprising "co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan)," a dose of 2400 mg/m^2 5-fluorouracil, and a dose of 200 mg/m^2 1 form or 400 mg/m^2 l+d form leucovorin for at least one cycle of two weeks. *Id.* at pp. 2-3. The Examiner also alleged that Conroy disclosed treatment of metastatic pancreatic cancer with oxaliplatin, irinotecan, leucovorin, and fluorouracil. *Id.* at p. 3. Furthermore, the Examiner alleged that "it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment" and that "[a]n ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy… ." *Id.*

Regarding the 60 mg/m^2 oxaliplatin dose recited in claim 1, the Examiner alleged that Conroy taught 85 mg/m^2 oxaliplatin[1], but not 60 mg/m^2 oxaliplatin. *Id.* at p. 4. The Examiner then pointed to Alcindor for allegedly teaching "that early studies of the development of oxaliplatin recognized a maximally efficient dose range of 45-67 mg/m^2 (Alcindor at section 6.1, 2nd paragraph)." *Id.* The Examiner alleged that the skilled artisan would have been motivated to follow the dosage range of 45-67 mg/m^2 referenced in Alcindor simply because oxaliplatin dosages are allegedly well known in the art (at page 22, section 6.1). *See* Office Action at pp. 4, 12. The Examiner argued that it "would have been prima facie obvious to one of ordinary skill in the art to have adjusted the dosage of oxaliplatin" and that "said artisan would have been so motivated because Alcindor also recognized adverse reactions of oxaliplatin… ." *Id.* at p. 4. Moreover, the Examiner alleged that the dosage of oxaliplatin is "recognized to be result effective" and that "it would have been prima facie obvious to have optimized the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Alcindor." *Id.*

Applicant respectfully traverses. Bayever discloses treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2), in combination with leucovorin (e.g., 400 mg/m^2 l+d form) and 5-fluorouracil (e.g., 2400 mg/m^2) to a patient once every two weeks. Conroy discloses treatment of patients with first-line metastatic pancreatic cancer by administering a different combination of therapeutic agents in different doses: Conroy administers a combination of 85 mg/m^2 oxaliplatin, 180 mg/m^2 non-liposomal irinotecan, 400 mg/m^2 leucovorin, 400 mg/m^2 fluorouracil as a bolus injection followed by 2400 mg/m^2 fluorouracil as a continuous infusion once every two weeks. Alcindor is a review article summarizing preclinical and clinical data involving oxaliplatin from multiple sources, including a Phase I, intra-patient dose escalation study of 45-67 mg/m^2 oxaliplatin, which is reported in Mathé et al., "A Phase I Trial of Trans-1-diamino-cyclohexane Oxalate-platinum (I-OHP)," Biomed Pharmacother, 40:372-376, 1986 ("Mathé Study") (cited in the accompanying IDS). *See* Alcindor at page 22, section 6.1 (reference 42). However, neither Bayever, Conroy, nor Alcindor teaches or suggests (solely or in combination) the claimed methods of treatment, including

[1] Applicant assumes that the Examiner's statement that Bayever teaches 85 mg/m^2 oxaliplatin was meant to refer to Conroy. *See* Office Action at p. 4. Applicant responds accordingly.

co-administering 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin, as recited in independent claims 1 and 19.

The Examiner has failed to establish a *prima facie* case of obviousness of the claimed methods of co-administering 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, leucovorin, and 5-fluorouracil once every two weeks to metastatic pancreatic cancer patients who have not previously been treated with an antineoplastic agent (claim 1) or gemcitabine (claim 19). The skilled artisan would not have been motivated to combine the 45-67 mg/m^2 dosage range of oxaliplatin referenced in Alcindor with the teachings of Bayever and Conroy for numerous reasons, some of which are summarized here and discussed more fully below.

First, the oxaliplatin dosage range of 45-67 mg/m^2 referenced in Alcindor (at page 22, section 6.1) was extrapolated from the "maximally efficient dose range" or "MEDR" identified in mice, not humans. Mathé at p. 373. Second, the Mathé Study that tested that dosage range of 45-67 mg/m^2 oxaliplatin included patients suffering from a variety of cancers, each of which is different from the claimed "metastatic adenocarcinoma of the pancreas." *Id.* at p. 373, Table I. Third, 21 of the 23 patients in the Mathé Study had undergone prior therapy (*id.*), whereas the method of claim 1 [or claim 19] is directed to patients who have not previously received an antineoplastic agent [or gemcitabine (claim 19)] to treat metastatic adenocarcinoma of the pancreas. Fourth, the Mathé Study evaluated escalating doses of 0.45 mg/m^2 up to 67 mg/m^2 oxaliplatin in each patient (*id.* at p. 374, Table II), unlike the set dose amount of oxaliplatin recited in the pending claims. Fifth, the Mathé Study evaluated oxaliplatin as a monotherapy, not as a combination therapy. *Id.* Sixth, in contrast to the "once every two week" coadministration schedule recited in the pending claims, the Mathé Study was designed such that each patient was to receive 4 escalating doses of oxaliplatin by the 11th day and each of the remaining 5 escalating doses at a three week interval. Seventh, Mathé concluded that a dose limiting toxicity of oxaliplatin was not reached in patients and that a further dose escalation phase II study involving doses beyond 45-67 mg/m^2 was planned. *Id.* at p. 375. This finding is consistent with results of another phase I dose escalation study summarized in Alcindor that recognized the maximum dose of oxaliplatin to be used in the clinic was 135 mg/m^2. Alcindor at page 22, section 6.1.

Factors such as cancer type, cancer severity, dose, dosing schedule, treatment following failure of prior therapies, drug-drug interactions, and overlapping toxicities could each affect

efficacy and tolerability of a particular cancer treatment method. The 45-67 mg/m^2 dosage range referenced in Alcindor was extrapolated from the MEDR established in animal studies (not human studies); the dosage range was studied in patient populations distinct from the claimed pancreatic cancer and that had undergone prior therapy; each patient received escalating doses of oxaliplatin as a monotherapy (not a set dose as a combination therapy); and based on the results, further dose escalations were planned. Each of those variables could affect treatment outcome. As a result, the 45-67 mg/m^2 dosage range of oxaliplatin referenced in Alcindor would have been of little to no value to the skilled artisan developing therapies for the first-line treatment of metastatic pancreatic cancer involving a combination of drugs.

Only by impermissible hindsight did the Examiner pick a dose range of oxaliplatin from the literature encompassing the claimed dose to piece with the disclosures of Bayever and Conroy. The Examiner did not, and cannot, explain why the skilled artisan would have been motivated to select and combine the dose range of 45-67 mg/m^2 oxaliplatin with Bayever and Conroy, in view of the context of its disclosure. In other words, the oxaliplatin dosing range cited by the Examiner cannot be separated from its concurrent teaching that it was extrapolated from the MEDR established in mice in early studies, tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and necessitated further dose escalations in a Phase II study.

"A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)). The Supreme Court has held that "it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007) (emphasis added). Further, "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *Id.* at 421 (emphasis added).

The requirement that the content of the prior art is determined at the time the invention was made is to avoid impermissible hindsight. MPEP § 2141.01 III. Furthermore, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 VI., citing *W.L. Gore & Assoc., Inc. v.*

Garlock, Inc. 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (followed e.g., by *Ex parte Alagappan*, 2017-005866, 2018 WL 3004459 (BPAI May 29, 2018). Thus, the Office must provide an objective reason why one of ordinary skill in the art *would have*, not merely *could have*, combined or modified the teachings of the cited art.

The dose range of 45-67 mg/m^2 oxaliplatin cited by the Examiner was used in an atypical Phase I study. Alcindor, section 6.1, 2nd paragraph, referenced by the Examiner at page 4 of the Office Action, states:

> The phase I studies evaluated activity and safety for a range of doses. Unlike the usual classical studies, in which patient cohorts are given progressively higher doses of the studied drug, Mathé et al. used a different design: Doses were escalated in each study patient until the maximally efficient dose range, defined as between 45 mg/m^2 and 67 mg/m^2 administered intravenously, was reached[42]. An absence of nephrotoxicity, setting oxaliplatin apart from cisplatin, was observed. Hints of activity against lung cancer, breast cancer, melanoma, and hepatoma were noted.

(Underlining added). Mathé (Reference 42) explains that the "starting and escalation doses were determined from the MEDR doses in mice ranging from 45 mg/m^2 (subcurative dose) to 67 mg/m^2 (subtoxic dose)." Mathé at p. 373, right column (citations omitted, underlining added).

The Mathé Study included only 23 patients and each patient suffered from a cancer distinct from metastatic pancreatic cancer. Table I of Mathé, reproduced below, lists breast cancer, lung cancer, and melanoma among the cancers afflicting the patients of the study, but not one had pancreatic cancer, let alone metastatic pancreatic cancer. In addition, all but two of the 23 patients had received prior therapy, whereas the method of claim 1 [or claim 19] is directed to patients who have not previously received an antineoplastic agent [or gemcitabine (claim 19)] to treat metastatic adenocarcinoma of the pancreas. "Most patients had exhausted all standard therapy and in two patients with no previous treatment the disease was the one for which no therapy of proven benefit was available. All but one had never received cisplatin before (Table I)." Mathé at p. 373, left column.

TABLE II

Patients characteristics.

Number of patients evaluated		23
	Sex ratio male/female	14/9
	Age range in years	21-77
	Average	51
Prior therapy		
	None	2
	Chemotherapy only	12
	Chemotherapy and hormonotherapy	1
	Chemotherapy and immunotherapy	3 (*)
	Radiotherapy only	2
	Chemotherapy and radiotherapy	4
Previous CDDP		1
Tumors:	Unknown primary	2
	Breast cancer	3
	Intraocular melanoma	1
	Lung cancer	1
	Malignant melanoma	9
	Primary liver tumor	3
	Prostate cancer	1
	Cholangiocarcinoma	1
	Small bowel carcinoma	1
	Schwanoma	1

(*) 1 patient received chemotherapy, radiotherapy and immunotherapy.

Id.

As noted above, the Mathé Study was designed for each patient to receive escalating doses of oxaliplatin as a monotherapy starting with 0.45 mg/m^2. *See* Mathé, page 374, Table II. According to Table II of Mathé (reproduced below), each patient was to receive 2 escalating doses of oxaliplatin the first day, a third escalated dose on the 4th day, a fourth escalated dose on the 11th day and each of the remaining 5 escalating doses was to be administered at a three-week interval.

TABLE II

Dose escalation table.
Modality of Administration: IV infusion.

0.45	Day 1
4.5	Day 1 afternoon
9	4
15	11
22.5	3 weeks interval
30	
45	
56	
67	

Id. The single drug, variable dose, and three-week interval design of the Mathé Study is vastly different from that of the pending claims, which recite co-administration of 60 mg/m^2 oxaliplatin with liposomal irinotecan and two other drugs once every two weeks.

From the results of the Mathé Study, the authors concluded that a dose limiting toxicity of oxaliplatin was not reached in patients and that a further dose escalation phase II study was planned:

> In conclusion we confirm the safety of [oxaliplatin] at the dose extrapolated from the MEDR in mice, dose at which antitumor responses have been observed. The fact that we did not reach a dose limiting toxicity is inherent to the new design of this phase I study, the objective of which was to confirm the tolerance of the high dose of MEDR. Further dose escalations are planned within the phase II study according to the Norton's model.

Mathé at p. 375, right column (underlining added). Consistent with Mathé's conclusion that further dose escalations should be tested, Alcindor discussed another phase I dose escalation trial that led to a "now accepted" maximum clinical dose of 135 mg/m^2:

> In a more conventional phase I trial[43], dose escalation reached 200 mg/m^2 delivered intravenously. At that dose level, the characteristic peripheral neuropathy was recognized leading to the recommendation, now accepted, that the maximum dose to be used in clinic be 135 mg/m^2 administered intravenously. Activity was also seen in various tumors, including some that had been pretreated with cisplatin.

Alcindor at page 22, section 6.1, 3rd paragraph (underlining added).

The Examiner alleged at page 4 of the Office Action that it would have been "prima facie obvious to one of ordinary skill in the art to have adjusted the dosage of oxaliplatin" without explaining why the skilled artisan would have looked to the dose range of 45-67 mg/m^2 oxaliplatin in the first place, particularly in view of the differences explained above between the claimed method and the Mathé Study, which actually tested the range of 45-67 mg/m^2 oxaliplatin referred to in Alcindor. Furthermore, the results of the Phase I studies led to conclusions that patients could tolerate much higher doses of oxaliplatin. *See* Alcindor at p. 22, section 6.1, 3rd pagragraph; Mathé at p. 375, right column. The Examiner's piecing together of doses from the prior art without providing an objective reason as to why one of ordinary skill in the art would have chosen the dose range as a starting point is impermissible hindsight. The 45-67 mg/m^2 dose range referenced in Alcindor that was extrapolated from the MEDR established in mice, that was tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and that necessitated further dose escalations in a Phase II study would have been of little to no value to the ordinarily skilled artisan developing first-line, co-therapies for metastatic pancreatic cancer.

Furthermore, even if a prima facie case of obviousness were to be established regarding any of the pending claims, which Applicant fervently traverses, one or more objective indicia of nonobvious would support a finding of nonobviousness. "Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing '(1) [t]hat the prior art taught away from the claimed invention… or (2) that there are new and unexpected results relative to the prior art.' *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004)." MPEP § 2144.05 III B. Other objective evidence of nonobviousness includes evidence of criticality, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc. *See* MPEP §§ 716.01(a) and 2145.

Alcindor and Mathé are examples of how the prior art taught away from the claimed dose of 60 mg/m^2 oxaliplatin and the cited dose range of 45-67 mg/m^2 oxaliplatin. As discussed above, Phase I studies led researchers to conclude that patients could tolerate oxaliplatin at doses of at least twice the cited range of 45-67 mg/m^2. "[C]haracteristic peripheral neuropathy was recognized [at 200 mg/m^2 delivered intravenously], leading to the recommendation, now

accepted, that the maximum dose to be used in clinic be 135 mg/m^2 administered intravenously." Alcindor, at p. 22, section 6.1. Such disclosure teaches away from the claimed 60 mg/m^2 oxaliplatin. While the right to present additional objective evidence of nonobviousness is reserved, Applicant respectfully asserts that the evidence of teaching away presented above negates any *prima facie* case of obviousness.

In sum, the Examiner has failed to establish a *prima facie* case of obviousness at least with respect to the claimed co-administration of a dose of "60 mg/m^2 oxaliplatin" by engaging in impermissible hindsight by cherry picking a dose range from the art. The Examiner did not explain why the skilled artisan would have been motivated to combine the dose range of 45-67 mg/m^2 oxaliplatin with Bayever and Conroy, when that oxaliplatin dose range was extrapolated from the MEDR established in mice in early studies, tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and necessitated further dose escalations in a Phase II study. For at least the reasons described above, the ordinarily skilled artisan would not have relied on the dose range referenced in Alcindor when developing first-line, co-therapies for metastatic pancreatic cancer.

Accordingly, the pending claims, which recite or otherwise incorporate "60 mg/m^2 oxaliplatin," are nonobvious over Bayever, Conroy, and/or Alcindor. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 5-8, 10 and 19 under 35 U.S.C. § 103 over Bayever in view of Conroy, and further in view of Alcindor.

Rejection of claims 4, 9, and 18

The Examiner rejected claims 4, 9, and 18 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy and further in view of Alcindor and Fleming et al. found at http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/ ("Fleming"). Office Action at pp. 6-7. The Examiner alleged that Fleming disclosed at the last sentence of the first paragraph that "the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics." *Id.* at p. 7. The Examiner alleged that in view of Fleming, an ordinarily skilled artisan would have been motivated to vary the order of administration of the combined methods of Bayever and Conroy. *Id.* at p 7.

Applicant respectfully traverses for at least the reasons discussed above with respect to claims 1 and 19, from which claims 4, 9, and 18 depend. As discussed, the Examiner has failed to establish a *prima facie* case of obviousness at least with respect to the claimed co-administration of a dose of "60 mg/m^2 oxaliplatin" by engaging in impermissible hindsight by cherry picking a dose range from the art. The Examiner did not explain why the skilled artisan would have been motivated to combine the dose range of 45-67 mg/m^2 oxaliplatin with Bayever and Conroy, when that oxaliplatin dose range was extrapolated from the MEDR established in mice in early studies, tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and necessitated further dose escalations in a Phase II study. For at least the reasons described above, the ordinarily skilled artisan would not have relied on the dose range referenced in Alcindor when developing first-line, co-therapies for metastatic pancreatic cancer.

Accordingly, claims 4, 9, and 18, which incorporate "60 mg/m^2 oxaliplatin," are nonobvious over Bayever, Conroy, Alcindor, and/or Fleming. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 9, and 18 under 35 U.S.C. § 103 over Bayever in view of Conroy, and further in view of Alcindor and Fleming.

Rejection of claims 11-15 and 21-22

The Examiner rejected claims 11-15 and 21-22 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy, further in view of Alcindor, and as evidenced by WO 2016/094402 ("Bayever II"). *Id.* at pp. 8-9. The Examiner alleged that while "Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12 and 21-22," Bayever II "evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE." The Examiner also alleged that claims 13-15 and 21-22 are rendered obvious because of the administration durations and cycles disclosed in Bayever. *Id.* at p. 9.

Applicant respectfully traverses for at least the reasons discussed above with respect to claims 1 and 19, from which claims 11-15 and 21-22 depend. As discussed, the Examiner has failed to establish a *prima facie* case of obviousness at least with respect to the claimed co-administration of a dose of "60 mg/m^2 oxaliplatin" by engaging in impermissible hindsight by cherry picking a dose range from the art. The Examiner did not explain why the skilled artisan would have been motivated to combine the dose range of 45-67 mg/m^2 oxaliplatin with Bayever

and Conroy, when that oxaliplatin dose range was extrapolated from the MEDR established in mice in early studies, tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and necessitated further dose escalations in a Phase II study. For at least the reasons described above, the ordinarily skilled artisan would not have relied on the dose range referenced in Alcindor when developing first-line, co-therapies for metastatic pancreatic cancer.

Accordingly, claims 11-15 and 21-22, which incorporate "60 mg/m^2 oxaliplatin," are nonobvious over Bayever, Conroy, Alcindor, and/or Bayever II. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 11-15 and 21-22 under 35 U.S.C. § 103 over Bayever in view of Conroy, further in view of Alcindor, and as evidenced by Bayever II.

III. Nonstatutory Double Patenting Rejections

The Examiner rejected claims 1, 4-15, 18-19, and 21-22 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-18 of U.S. Patent No. 9,492,442 ("the '442 Patent") in view of Conroy, and further in view of Alcindor. *Id.* at pp. 11-12. The Examiner alleged that the "issued claims recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin." *Id.* at pp. 8-9. The Examiner further alleged that "it would have been prima facie obvious to have used oxaliplatin in the issued method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro*." *Id* at p. 11. The Examiner argued that Alcindor allegedly "taught that early studies of the development of oxaliplatin recognized a maximally efficient dose range of 45-67 mg/m^2" and that "a skilled artisan would be motivated, and guided, by the art to follow dosage regimens that are well known in the art." *Id.* at pp. 11, 12.

Applicant respectfully traverses. Coadministration of a dose of 60 mg/m^2 oxaliplatin would not have been an obvious variation of any of claims 1-18 of the '442 Patent for at least the reasons discussed above. The Examiner did not explain why the skilled artisan would have been motivated to combine the dose range of 45-67 mg/m^2 oxaliplatin with Bayever and Conroy, when that oxaliplatin dose range was extrapolated from the MEDR established in mice in early studies, tested in completely different patient populations at a different dosing regime and schedule from that of the claimed methods, and necessitated further dose escalations in a Phase II

study. For at least the reasons described above, the ordinarily skilled artisan would not have relied on the dose range referenced in Alcindor when developing first-line, co-therapies for metastatic pancreatic cancer. Accordingly, the pending claims are not obvious variations of issued claims 1-18 of the '442 Patent.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-18 of the '442 Patent, in view of Conroy, and further in view of Alcindor.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

MCNEILL BAUR PLLC.

Dated: February 11, 2019

By: /Mary R. Henninger, PhD/
Mary R. Henninger, PhD
Reg. No. 56,992
404-891-1400

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application. Please amend the claims as follows:

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
   a. 60 mg/m^2 of liposomal irinotecan,
   b. 60 mg/m^2 oxaliplatin,
   c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
   d. 2,400 mg/m^2 5-fluorouracil;

   to treat the metastatic adenocarcinoma of the pancreas in the human patient.

2. (Canceled)

3. (Canceled)

4. (Original) The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

5. (Original) The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

6. (Original) The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

7. (Original) The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

8. (Original) The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

9. (Original) The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. (Original) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

11. (Currently Amended) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes composed ~~vesicles consisting~~ of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

12. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

13. (Previously Presented) The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

14. (Previously Presented) The method of claim 19, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

15. (Previously Presented) The method of claim 14, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered

prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

16. (Canceled)

17. (Canceled)

18. (Previously Presented) The method of claim 19, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

19. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil;

    to treat the metastatic adenocarcinoma of the pancreas in the human patient.

20. (Canceled)

21. (Currently Amended) The method of claim 1[[12]], wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

22. (Currently Amended) The method of claim 19[[14]], wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

23. (New) The method of claim 1, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Eliel BAYEVER et al.	Group Art Unit: 1612
Application No.: 15/809,815	Examiner: Celeste A. Roney
Filed: November 10, 2017	Confirmation No.: 5137
For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Via EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Roney:

In reply to the Final Office Action mailed September 11, 2018, the period for response having been extended to February 11, 2019, by a request for extension of 2 months and fee payment filed concurrently herewith, please amend the above-identified application as follows:

Amendments to the Claims begin at page 2.

Remarks begin at page 6.

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 01208-0007-01US

Application Number: 15/809,815

Filed: November 10, 2017

For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

Art Unit: 1612

Examiner: Celeste A. Roney

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☑	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 600
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 56,992.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Mary R. Henninger/ — Signature

February 11, 2019 — Date

Mary R. Henninger — Typed or printed name

404-891-1400 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1629
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	1	Extra J, et al., "Phase I Study of Oxaliplatin in Patients with Advanced Cancer," Cancer Chemother Pharmacol. 25 (4):299-303 (1990).
	2	Mathé G, et al., "A Phase I Trial of Trans-1-diamino-cyclohexane Oxalate-platinum (l-OHP)," Biomed Pharmacother, 40:372-6 (1986).

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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2019-02-11
Name/Print	Mary R. Henninger	Registration Number	56992

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	1	Chen L, et al., "Phase I Study of Liposome Encapsulated Irinotecan (PEP02) in Advanced Solid Tumor Patients," Poster presented at the ASCO meeting of May 30 - June 3, 2008, Chicago, Illinois, 9 pages.
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	23	Dean A, et al., "A Randomized, Open-label, Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens versus nab-Paclitaxel Plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma (mPAC)." Poster presented at the Gastrointestinal Cancers Symposium ASCO 2016, 11 pages.
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	25	Gaddy D., "Preclinical Anti-tumor Activity of Nanoliposomal Irinotecan (Nal-IRI, MM-398) + 5-FU + Oxaliplatin in Pancreatic Cancer." Abstract presented at AACR 2016, 1 page.
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	29	Kalra A, et al., "Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion," Cancer Res. Author queries on manuscript, pages 1-11 (2014), 13 total pages.
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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2019-02-13
Name/Print	Mary R. Henninger	Registration Number	56992

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/08a (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	01208-0007-01US

	1	U.S. Patent Application No. 11/121,294: 2009-08-17 Nonfinal Office Action, 33 pages.
	2	U.S. Patent Application No. 11/121,294: 2010-03-12 Final Office Action, 15 pages.
	3	U.S. Patent Application No. 11/121,294: 2010-05-19 Advisory Action, 3 pages.
	4	U.S. Patent Application No. 11/121,294: 2010-08-04 Nonfinal Office Action, 14 pages.
	5	U.S. Patent Application No. 11/121,294: 2010-12-06 Final Office Action, 17 pages.
	6	U.S. Patent Application No. 11/121,294: 2011-04-13 Nonfinal Office Action, 10 pages.
	7	U.S. Patent Application No. 11/121,294: 2011-07-12 Examiner Interview Summary, 3 pages.
	8	U.S. Patent Application No. 11/121,294: 2011-11-23 Final Office Action, 20 pages.
	9	U.S. Patent Application No. 11/601,451: 2010-01-11 Nonfinal Office Action, 14 pages.
	10	U.S. Patent Application No. 11/601,451: 2010-08-27 Final Office Action, 17 pages.
	11	U.S. Patent Application No. 11/601,451: 2011-07-12 Examiner Interview Summary, 4 pages.

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	Attorney Docket Number	01208-0007-01US

	12	U.S. Patent Application No. 13/416,204: 2012-05-08 Pre-Interview Communication, 4 pages.	
	13	U.S. Patent Application No. 13/416,204: 2012-06-29 Interview Summary and First Action Interview Office Action, 6 pages.	
	14	U.S. Patent Application No. 13/654,373: 2013-08-12 Nonfinal Office Action and Interview Summary, 10 pages.	
	15	U.S. Patent Application No. 14/151,632: 2016-04-18 Nonfinal Office Action, 9 pages.	
	16	U.S. Patent Application No. 14/175,365: 2014-06-26 Nonfinal Office Action, 20 pages.	
	17	U.S. Patent Application No. 14/406,776: 2016-02-26 Nonfinal Office Action, 9 pages.	
	18	U.S. Patent Application No. 14/406,776: 2016-04-25 Response to Non-final Office Action mailed February 26, 2016, 71 pages.	
	19	U.S. Patent Application No. 14/632,422: 2017-01-10 Nonfinal Office Action, 18 pages.	
	20	U.S. Patent Application No. 14/812,950: 2015-10-02 Pre-Interview Communication, 3 pages.	
	21	U.S. Patent Application No. 14/812,950: 2015-10-22 Preliminary amendment in response to Pre-Interview Communication mailed October 2, 2015, 7 pages.	
	22	U.S. Patent Application No. 14/844,500: 2015-12-16 Nonfinal Office Action, 25 pages.	

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	23	U.S. Patent Application No. 14/844,500: 2016-02-25 Response to Non-final Office Action mailed December 16, 2015, 15 pages.	
	24	U.S. Patent Application No. 14/851,111: 2016-02-25 Nonfinal Office Action, 13 pages.	
	25	U.S. Patent Application No. 14/851,111: 2016-05-12 Response to Non-final Office Action mailed February 25, 2016, 71 pages.	
	26	U.S. Patent Application No. 14/879,302: 2016-08-15 Nonfinal Office Action, 30 pages.	
	27	U.S. Patent Application No. 14/879,302: 2016-12-15 Nonfinal Office Action, 14 pages.	
	28	U.S. Patent Application No. 14/879,358: 2015-12-28 Nonfinal Office Action, 20 pages.	
	29	U.S. Patent Application No. 14/879,358: 2016-07-12 Nonfinal Office Action, 14 pages.	
	30	U.S. Patent Application No. 14/964,239: 2016-11-04 Nonfinal Office Action, 21 pages.	
	31	U.S. Patent Application No. 14/964,239: 2017-04-26 Examiner Interview Summary, 2 pages.	
	32	U.S. Patent Application No. 14/964,239: 2017-06-21 Nonfinal Office Action, 16 pages.	
	33	U.S. Patent Application No. 14/964,239: 2017-12-11 Nonfinal Office Action, 15 pages.	

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	Attorney Docket Number	01208-0007-01US

	34	U.S. Patent Application No. 14/964,571: 2017-02-13 Nonfinal Office Action, 8 pages.	
	35	U.S. Patent Application No. 14/964,571: 2017-11-01 Final Office Action, 14 pages.	
	36	U.S. Patent Application No. 14/964,571: 2018-09-25 Nonfinal Office Action, 12 pages.	
	37	U.S. Patent Application No. 14/965,140: 2016-03-10 Nonfinal Office Action, 24 pages.	
	38	U.S. Patent Application No. 14/965,140: 2016-07-13 Interview Summary and Nonfinal Office Action, 14 pages.	
	39	U.S. Patent Application No. 14/965,140: 2016-12-19 Nonfinal Office Action, 9 pages.	
	40	U.S. Patent Application No. 14/966,458: 2016-12-06 Nonfinal Office Action, 34 pages.	
	41	U.S. Patent Application No. 14/966,458: 2017-04-27 Examiner Interview Summary, 2 pages.	
	42	U.S. Patent Application No. 14/979,666: 2016-12-09 Nonfinal Office Action, 20 pages.	
	43	U.S. Patent Application No. 15/059,640: 2016-12-02 Nonfinal Office Action, 9 pages.	
	44	U.S. Patent Application No. 15/227,561: 2017-07-14 Nonfinal Office Action, 25 pages.	

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	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	45	U.S. Patent Application No. 15/227,561: 2018-04-26 Nonfinal Office Action, 13 pages.	
	46	U.S. Patent Application No. 15/227,561: 2018-12-10 Final Office Action, 18 pages.	
	47	U.S. Patent Application No. 15/227,631: 2017-07-17 Nonfinal Office Action, 24 pages.	
	48	U.S. Patent Application No. 15/227,631: 2018-04-10 Nonfinal Office Action, 13 pages.	
	49	U.S. Patent Application No. 15/227,631: 2018-08-31 Nonfinal Office Action, 15 pages.	
	50	U.S. Patent Application No. 15/227,631: 2018-12-19 Final Office Action, 15 pages.	

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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2019-02-13
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	1	U.S. Patent Application No. 15/241,106: 2016-10-28 Pre-Interview Communication, 4 pages.
	2	U.S. Patent Application No. 15/241,106: 2016-12-29 Nonfinal Office Action, 15 pages.
	3	U.S. Patent Application No. 15/241,106: 2017-07-10 Final Office Action, 16 pages.
	4	U.S. Patent Application No. 15/241,128: 2016-11-25 Nonfinal Office Action, 6 pages.
	5	U.S. Patent Application No. 15/296,536: 2017-03-08 Nonfinal Office Action, 6 pages.
	6	U.S. Patent Application No. 15/331,393: 2017-01-19 Pre-Interview Communication, 4 pages.
	7	U.S. Patent Application No. 15/331,393: 2017-03-20: Examiner's Interview Summary and First Action Interview Office Action Summary, 5 pages.
	8	U.S. Patent Application No. 15/331,648: 2017-01-19 Pre-Interview Communication, 4 pages.
	9	U.S. Patent Application No. 15/331,648: 2017-03-17 Examiner's Interview Summary, 3 pages.
	10	U.S. Patent Application No. 15/337,274: 2017-03-24 Nonfinal Office Action, 10 pages.
	11	U.S. Patent Application No. 15/341,377: 2017-01-30 Nonfinal Office Action, 12 pages.

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	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	12	U.S. Patent Application No. 15/341,377: 2017-04-18 Final Office Action, 13 pages.	
	13	U.S. Patent Application No. 15/341,619: 2017-04-03 Pre-Interview Communication, 3 pages.	
	14	U.S. Patent Application No. 15/363,761: 2017-01-18 Nonfinal Office Action, 15 pages.	
	15	U.S. Patent Application No. 15/363,761: 2017-08-01 Final Office Action, 18 pages.	
	16	U.S. Patent Application No. 15/363,761: 2017-12-14 Examiner Interview Summary, 3 pages.	
	17	U.S. Patent Application No. 15/363,923: 2017-02-01 Nonfinal Office Action, 24 pages.	
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	19	U.S. Patent Application No. 15/363,978: 2017-02-07 Nonfinal Office Action, 16 pages.	
	20	U.S. Patent Application No. 15/363,978: 2017-08-21 Final Office Action, 19 pages.	
	21	U.S. Patent Application No. 15/363,978: 2017-12-14 Examiner Interview Summary, 3 pages.	
	22	U.S. Patent Application No. 15/364,021: 2017-03-09 Nonfinal Office Action, 18 pages.	

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	23	U.S. Patent Application No. 15/364,021: 2017-10-04 Final Office Action, 20 pages.	
	24	U.S. Patent Application No. 15/375,039: 2018-02-16 Nonfinal Office Action, 11 pages.	
	25	U.S. Patent Application No. 15/403,441: 2017-12-21 Nonfinal Office Action, 9 pages.	
	26	U.S. Patent Application No. 15/645,645: 2017-12-01 Nonfinal Office Action, 16 pages.	
	27	U.S. Patent Application No. 15/652,513: 2017-12-20 Nonfinal Office Action, 13 pages.	
	28	U.S. Patent Application No. 15/661,868: 2017-12-01 Nonfinal Office Action, 15 pages.	
	29	U.S. Patent Application No. 15/664,930: 2017-12-20 Nonfinal Office Action, 7 pages.	
	30	U.S. Patent Application No. 15/664,976: 2018-09-11 Nonfinal Office Action, 23 pages.	
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	33	U.S. Patent Application No. 15/852,551: 2019-01-11 Nonfinal Office Action, 5 pages.	

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	34	U.S. Patent Application No. 15/967,638: 2019-01-14 Nonfinal Office Action, 14 pages.

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CERTIFICATION STATEMENT

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2019-02-13
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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(54) Title: METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

(57) Abstract: Combination therapy regimens including liposomal irinotecan, oxaliplatin and 5-fluorouracil are useful in the treatment of pancreatic cancer, including treatment of patients diagnosed with previously untreated metastatic adenocarcinoma of the pancreas. The combination therapy can include the administration of liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil once every two weeks.

METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

RELATED APPLICATIONS

This patent application claims priority to each of the following pending U.S. provisional patent applications, each incorporated herein by reference in their entirety: 62/208,209 (filed August 21, 2015), 62/216,736 (filed September 10, 2015), 62/273,244 (filed December 30, 2015), 62/281,473 (filed January 21, 2016), 62/302,341 (filed March 2, 2016), 62/323,245 (filed April 15, 2016) and 62/343,313 (filed May 31, 2016).

TECHNICAL FIELD

This disclosure relates to novel therapies useful in the treatment of pancreatic cancer, including the use of liposomal irinotecan in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer.

BACKGROUND

Pancreatic cancer is chemotherapy-resistant, with an extremely poor prognosis. It is the fourth leading cause of cancer death in the United States; the 5-year survival rate is 6%. The incidence of pancreatic cancer has increased during the past several decades and in 2014, an estimated 46,420 patients were diagnosed with pancreatic cancer and 39,590 died. Pancreatic cancer is projected to surpass liver, breast, prostate, and colorectal cancers to become the second-leading cause of cancer-related death by 2030. These statistics reflect the dire nature of the disease and lack of effective therapies. The location of the tumor results in few early symptoms and is often diagnosed at a late stage as a result. The absence of effective screening tools, and a limited understanding of risk factors, means that patients have advanced or metastatic disease at the time of diagnosis. Given the poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, new treatment options are still needed.

Tolerability of multi-drug regimens is important in cancer treatment. The longer the duration of manageable treatment should translate into improved outcome due to longer

drug exposure. During the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX). However, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status (i.e. ECOG performance score of 0 or 1). With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity. Therefore, if equally effective double regimens can be identified, patients may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit. Although the FOLFIRINOX regimen has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011, there are some concerns about the toxicity associated with FOLFIRINOX. One dose regimen of FOLFIRINOX is 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, and fluorouracil at a dose of 400 mg/m^2 administered by IV bolus followed by a continuous infusion of 2400 mg/m^2. Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules.

CPT-11 is irinotecan hydrochloride trihydrate, marketed as Camptosar® in the United States. MM-398 is a liposomal irinotecan and is marketed in the U.S. as the FDA-approved product ONIVYDE® in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

SUMMARY

Improved antineoplastic therapies for the treatment of pancreatic cancer provide the administration of liposomal irinotecan in combination with oxaliplatin and 5-fluorouracil to patients with previously untreated pancreatic cancer (e.g., untreated metastatic pancreatic adenocarcinoma, or mPAC). The 5-fluorouracil can be administered in combination with leucovorin. The improved antineoplastic therapies can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens.

A method of treating pancreatic cancer can comprise the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient. Optionally, leucovorin can also be administered prior to each administration of the 5-fluorouracil. Each administration of the liposomal irinotecan can be administered in a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein). A total of 2,400 mg/m^2 5-fluorouracil can be administered over 46 hours starting on each day when the liposomal irinotecan is administered. A total of 60, 75 or 85 mg/m^2 oxaliplatin can be administered on each day the liposomal irinotecan is administered. A total of 200 mg/m^2 (l) leucovorin can be administered prior to each administration of the 5-flurouracil (e.g., optionally administered as 400 mg/m^2 of (l+d) leucovorin). The antineoplastic therapy can be administered starting on days 1 and 15 of a 28-day treatment cycle, with the liposomal irinotecan, oxaliplatin, and optionally leucovorin administered on days 1 and 15 and initiating the 46-hour administration of the 5-fluorouracil on days 1 and 15.

The invention is based in part on several pre-clinical discoveries. First, liposomal irinotecan improved anti-tumor activity of the topoisomerase 1 inhibitor SN-38 (an active metabolite of irinotecan) relative to exposure-matched doses of non-liposomal irinotecan. Second, liposomal irinotecan combined with 5-fluorouracil and oxaliplatin consistently improved tumor growth inhibition and survival in mouse xenograft models of pancreatic cancer relative to non-liposomal irinotecan, without exacerbating the baseline toxicities of these agents.

In addition, the invention is based in part on the discovery that the administration of a dose of 80 mg/m^2 liposomal irinotecan was not well tolerated in humans when administered in combination with 60 mg/m^2 oxaliplatin, 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 (l+d) leucovorin. Accordingly, preferred methods of treating (previously untreated) pancreatic cancer provide for the administration of a human-tolerated antineoplastic therapy once every two weeks, where each administration of the antineoplastic therapy is a combination of the antineoplastic agents liposomal irinotecan, oxaliplatin and 5-fluorouracil provided herein. Preferably, the antineoplastic therapy administered once every two weeks consists of: (a) a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein), (b) a total dose of 60-85 mg/m^2

oxaliplatin (including, e.g., 60 or 85 mg/m^2), and (c) a total of 2,400 mg/m^2 5-fluorouracil optionally administered in combination with leucovorin. Optionally, the combination can include administration of a total of 200 mg/m^2 (l) leucovorin (optionally administered as 400 mg/m^2 of (l+d) leucovorin), prior to initiating the administration of the 5-fluorouracil. Preferably, no other antineoplastic agent is administered during the antineoplastic therapy, other than amounts of SN-38 produced within the patient from the liposomal irinotecan, after administration of the liposomal irinotecan. For example, the antineoplastic therapy can be administered without (non-liposomal) CPT-11 irinotecan. Preferably, the liposomal irinotecan, oxaliplatin, and (optionally) leucovorin are consecutively administered as separate infusions on a single (first) day and the 5-fluorouracil is administered starting on the first day after the administration of the leucovorin (if administered) and continuing into the following day (e.g., over a total of 46 hours).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a graph showing the simulated levels of the active irinotecan metabolite SN-38 over time based on liposomal irinotecan human clinical biopsy data and human clinical trial data.

Figure 1B is a schematic showing how the tumor exposure of SN-38 over time observed with liposomal irinotecan (MM-398) is prolonged compared to SN-38 tumor exposure from non-liposomal irinotecan (CPT-11).

Figure 1C is a graph showing the percent relative cell growth inhibition of SN-38 based on various times of total SN-38 cell exposure for 5 different cell lines.

Figure 1D is a graph showing the percent relative cell growth inhibition of the cell lines tested in Figure 1C at different exposure times (4 hours or 48 hours) for different combinations of SN-38 with 5-fluorouracil (5-FU) or oxaliplatin (oxali).

Figure 2A is a graph showing the cell viability as a function of SN-38 exposure for BxPC-3 pancreatic cancer cells.

Figure 2B is a graph showing the cell viability as a function of SN-38 exposure for CFPAC-1 pancreatic cancer cells.

Figure 3A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with individual antineoplastic agents: including 5-fluorouracil (5FU), oxaliplatin (Ox), (non-liposomal) irinotecan (IRI) and MM-398 liposomal irinotecan (nal-IRI).

Figure 3B is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with various combinations of antineoplastic agents: (non-liposomal) irinotecan (IRI) and 5FU; (non-liposomal)irinotecan (IRI), oxaliplatin and 5FU; MM-398 liposomal irinotecan (nal-IRI) and 5FU; and 398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU.

Figure 4A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 4B is a graph showing the tumor volume over time measured in a CFPAC-1 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 5A is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5B is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the MM-398 containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU), MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5C is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the oxaliplatin containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6A is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (nal-IRI) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan).

Figure 6B is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6C is a graph of the progression free survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6D is a graph of the overall survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 7 is a graph showing the tumor volume measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 8 is a table showing the results obtained from a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal

irinotecan alone, non-liposomal irinotecan alone (monotherapy), MM-398 liposomal irinotecan in combination with 5FU (NAPOLI, double therapy), MM-398 liposomal irinotecan in combination with 5FU + oxaliplatin (NAPOX, triple therapy) and non-liposomal irinotecan combined with oxaliplatin and 5-fluorouracil (FOLFIRINOX).

Figure 9 is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of a saline control, liposomal irinotecan (nal-IRI), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin on days 0, 7, 14 and 21.

Figure 10A is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given together on the same day.

Figure 10B is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given sequentially on separate successive days with the MM-398 administered on day 1 and the oxaliplatin administered on day 2.

Figures 11A, 11B and 11C are bar graphs depicting hematological toxicities observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: A. White blood cells; B. Neutrophils; and C. Lymphocytes.

Figures 11D, 11E and 11F is bar graphs depicting liver enzyme levels observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: D. aspartate aminotransferase (AST); E. alanine transaminase (ALT); F. alkaline phosphatase (ALKP).

Figure 12 is a schematic of methods of treating pancreatic cancer, including methods comprising the administration of liposomal irinotecan, oxalipaltin, 5-fluorouracil and leucovorin.

DETAILED DESCRIPTION

Unless otherwise indicated, the dose of liposomal irinotecan or irinotecan liposome as recited herein refers to the amount of irinotecan hydrochloride trihydrate providing an amount of irinotecan encapsulated in the liposome of the liposomal irinotecan or irinotecan liposome. For example, a dose of 60 mg/m^2 liposomal irinotecan refers to an amount of the liposomal irinotecan providing the same amount of liposome encapsulated irinotecan that is present in 60 mg/m^2 of irinotecan hydrochloride trihydrate, and is equivalent to a dose of about 50 mg/m^2 of liposomal irinotecan based on the amount of the irinotecan free base encapsulated in the liposomal irinotecan.

As used herein, unless otherwise indicated, the term "nal-IRI" (nanoliposomal irinotecan) and "MM-398" refer to a form of liposomal irinotecan. The term "CPT-11" refers to (non-liposomal) irinotecan hydrochloride trihydrate.

As used herein, "5-FU" and "5FU" and used interchangeably and refer to 5-fluorouracil.

All cited documents are incorporated herein by reference.

Using pancreatic cancer cell lines (Example 1), we demonstrated enhanced cell death when liposomal irinotecan treatment is simulated using prolonged exposure of SN-38 (the active metabolite of irinotecan) in combination with 5-FU and oxaliplatin. Figure 1 shows that prolonged exposure of SN-38 simulates MM-398 treatment in vitro. Referring to Figure 1A, MM-398 treatment results in prolonged tumor exposure to the active metabolite, SN-38, compared to non-liposomal irinotecan (CPT-11). Referring to Figure 1B, prolonged low-dose exposure of SN-38 mimics MM-398 tumor delivery in vitro. Referring to Figure 1C, prolonged low-dose exposure resulted in greater cell growth inhibition in multiple pancreatic cancer cell lines. The graph comprises four sections, and for each section the cell line data is presented with AsPC-1 data at the top, followed next by BxPC-3, Capan-2, CFPAC-1, and finally MaPaCa-2 on the bottom. Referring to Figure 1D, the benefit of prolonged exposure to low concentrations of SN-38 was also observed when combined with

5-FU (20.7 mM for 48h) or oxaliplatin (12.3 mM for 4h). Both combinations also increased sensitivity of resistance cell lines to prolonged low-dose SN-38.

Figure 2 is two line graphs that depict cell viability following treatment with SN-38 as a single agent or the combination of SN-38 and oxaliplatin. BxPC-3 (Figure 2A) or CFPAC-1 (Figure 2B) cells were treated for 4h or 72h, washed and then incubated for an additional 24h or 144h with fresh media, following which cell viability was assessed. The data traces are labeled "1" (SN-38 alone for four hours followed by a 24 hour incubation; "2" SN-38 + oxaliplatin for four hours followed by a 24 hour incubation; "3" SN-38 alone for 72 hours followed by a 144 hour incubation; and "4" SN-38 + oxaliplatin for 72 hours followed by a 144 hour incubation. Treatment of the cells with a combination of SN-38 and oxaliplatin decreased the IC-50 when cells were treated for 4h only as compared to treatment with single agents in both cell lines tested.

Testing of cell line-derived and patient-derived xenograft models of pancreatic cancer in Example 2 demonstrated improved anti-tumor activity of liposomal irinotecan relative to exposure-matched doses of non-liposomal irinotecan. In the mouse animal studies in Example 2, a dose of "x" mg/kg liposomal irinotecan provides about the same exposure to the topoisomerase 1 inhibitor (irinotecan and/or SN-38) as a dose of "5x" non-liposomal irinotecan (CPT-11). The liposomal irinotecan consistently improved tumor growth inhibition and survival relative to non-liposomal irinotecan in preclinical models, both as a monotherapy and in combination with 5-FU and oxaliplatin. The addition of MM-398 to 5-FU and/or oxaliplatin did not exacerbate the baseline toxicities of these agents, including weight loss and neutropenia, and tolerability could be further improved by delaying the administration of oxaliplatin to 1 day post-MM-398. These findings illustrate the therapeutic potential of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and support an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2).

An animal model of the FOLFIRINOX regimen was tested against the MM-398 + 5-FU/LV + oxaliplatin regimen in a pancreatic tumor xenograft mouse model. Liposomal irinotecan (MM-398) performed better than conventional (non-liposomal) irinotecan (CPT-11) at equivalent exposure doses (5 mg/kg MM-398 vs. 25 mg/kg free IRI) in the BxPC-3 pancreatic

xenograft cancer models (Example 2) either alone (e.g., Figure 3A), or in combination with oxaliplatin and/or 5-FU (e.g., Figure 3B).

In the mouse model tested in Example 2, efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3) was evaluated. Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with free irinotecan (IRI), MM-398, 5-FU, oxaliplatin (Ox) or control was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. Figure 3A depicts a line graph representing tumor growth after treatment with various individual treatment agents. Figure 3B depicts a line graph representing tumor growth after treatment with various combinations of treatment agents.

Efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3). Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. In comparison to Figure 4A (discussed below), doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU demonstrate that the MM-398-containing doublet and triplet regimens inhibit tumor growth significantly better than the IRI-containing regimens. The addition of oxaliplatin to the doublet combinations of FOLFIRI or MM-398+5-FU/LV causes a slight increase in tumor growth inhibition (Figure 3B: compare IRI + 5FU to IRI + 5FU +Ox for FOLFIRI vs. FOLFIRINOX; compare nal-IRI + 5FU to nal-IRI + 5FU + Ox for MM-398+5-FU/LV vs. MM-398+5-FU/LV+Ox). However, comparison of FOLFIRI versus the MM-398+5-FU/LV doublet (IRI + 5FU vs. nal-IRI + 5FU), and FOLFIRINOX vs. the MM-398+5-FU/LV+Ox triplet (IRI + 5FU +Ox vs. nal-IRI + 5FU + Ox), demonstrates significantly more tumor growth inhibition with the MM-398-containing regimens. Further, the MM-398-containing doublet regimen performed better than the FOLFIRINOX triplet (nal-IRI + 5FU vs. IRI + 5FU +Ox), owing to the improved efficacy of MM-398 compared to conventional irinotecan.

Single agent results of the individual treatments are shown in Figure 4A, demonstrating that MM-398 significantly inhibits tumor growth compared to free IRI. Figures 4A and 4B are

two line graphs depicting tumor growth in mouse xenograft models following intravenous treatment with saline (control, circles), 5 mg/kg oxaliplatin (triangles), 5 mg/kg MM-398 (light squares), or the combination of BxPC-3 (Figure 4A) or CFPAC-1 (Figure 4B) tumor cells were implanted subcutaneously in mice. Treatment was initiated after tumors were well established, and treatments were given four times (BxPC-3 model) or three times (CFPAC-1 model) at the time points indicated by dashed lines on the graphs.

Figures 5A, 5B, 5C, 6A, 6B, 6C, 6D and 7 are graphs obtained by measuring tumor growth inhibition in mice following various treatments. Tumor cells (PDX model 19015) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone, or in combination with 5-FU or 5-FU + oxaliplatin, was initiated. Treatment doses are indicated in the figure beside each treatment, and were given 4 times.

Figures 5A-5C are three line graphs depicting tumor growth inhibition in mice following various treatments. Tumor cells, PDX 19015 model, were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan as monotherapy, or in combination with 5-FU and Oxaliplatin, was initiated. Treatment doses are indicated in the legend beside each treatment, and were given four times, at time points indicated by dashed lines on the graphs. The addition of 5-FU to MM-398 or non-liposomal irinotecan significantly improved tumor growth inhibition relative to the respective monotherapies. The addition of oxaliplatin to MM-398 + 5-FU further improves response by significantly delaying tumor progression as compared to MM-398 monotherapy. The delay in tumor progression was not significant in the group treated with the double therapy of MM-398 + 5-FU. Figure 5A is a line graph comprising data from all of the combinations (both those with MM-398 and those with irinotecan), and shows that the combination of MM-398, oxaliplatin, and 5-FU resulted in the most inhibition of tumor growth (lowest line trace), although the combination of MM-398 and 5-FU also inhibited tumor growth (next lowest line). Figure 5B is a line graph comprising data from the MM-398 combinations only (no irinotecan combinations or control line) for the purpose of comparison. As can be seen in the graph, the triple combination treatment resulted in the most tumor growth inhibition (lowest line), and the double combination of irinotecan and 5-FU (middle line) was better than MM-398 alone

(highest line) in inhibiting tumor growth. Figure 5C is a subset of the same data that allows comparison of the oxaliplatin combinations to the saline control.

Figure 6A is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (MM-398) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan). The data in Figure 6A shows a significantly greater reduction in the percent tumor volume change for administration of 10 mg/kg liposomal irinotecan (MM-398) compared to non-liposomal irinotecan (CPT-11) at 50 mg/kg, each administered on days 0, 7, 14 and 21 followed by observation for a total of about 60 days. Figure 6B is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (MM-398), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU. Mice receiving the combination of liposomal irinotecan (MM-398, also called MM-398) with 5FU and oxaliplatin on days 0, 7, 14 and 21 showed significantly reduced tumor volume percent change through the observation period of about 60 days, compared to mice receiving the combination of non-liposomal irinotecan (CPT-11) with oxaliplatin and 5-FU on days 0, 7, 14 and 21. Referring to Figure 6C, the addition of oxaliplatin to MM-398 + 5-FU significantly improves progression free survival of mice bearing PDX 19015 tumors, as compared to the control group and MM-398 monotherapy. The difference between MM-398 + 5FU and MM-398 monotherapy is not statistically significant. Referring to Figure 6D, the addition of 5-FU and oxaliplatin to MM-398 significantly improve overall survival relative to the control group. No benefit of added 5-FU or oxaliplatin was observed with non-liposomal irinotecan. Referring to Figure 7, the addition of oxaliplatin to MM-398 + 5-FU significantly delays tumor progression relative to MM-398 monotherapy, as indicated by significantly reduced tumor volume at day 35.

Figure 8 is a table showing results of tumor growth and survival in mice following various treatments. Tumor cells (PDX 19015 model) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone (monotherapy), or in combination with 5-FU (NAPOLI, double therapy) or 5-FU + oxaliplatin (NAPOX, triple therapy), was initiated.

Mice treated with the triple therapy, NAPOX (50%) had the best Overall Response Rate (ORR), as compared to double NAPOLI (38%), or monotherapy MM-398 monotherapy (0%). Further, triple therapy treated mice also had a better Disease Control Rate (DCR): NAPOX (75%), NAPOLI (63%), MM-398 monotherapy (38%), and Progression Free Survival (PFS): NAPOX was 47 days, relative to 36.5 days for NAPOLI and 12 days for MM-398 monotherapy. NAPOX PFS was significantly better than the monotherapy, whereas NAPOLI is not significantly better than the monotherapy. Notably, the combination of liposomal irinotecan with 5FU and oxaliplatin was better tolerated than the combination of an SN-38 exposure-matched dose of non-liposomal irinotecan with 5FU and oxaliplatin in a mouse tolerability study over 100 days. Figure 9 is a graph showing the body weight of mice after administration of various regimens: a saline control, liposomal irinotecan (MM-398), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin. Liposomal irinotecan improved tolerability in a mouse model following repeated dosing in mice relative to non-liposomal irinotecan when combined with 5-FU and oxaliplatin. Significance was determined by ordinary 2-way analysis of variance (ANOVA). The regimens were administered on days 0, 7, 14 and 21 of the study. The administration of 10 mg/kg liposomal irinotecan and the 50 mg/kg dose of non-liposomal free irinotecan (CPT11) provide a comparable dose of SN-38 to tumor cells in the mouse model.

The tolerability of combinations of MM-398 liposomal irinotecan and oxaliplatin was improved in mouse models when the oxaliplatin was administered one day after the administration of the MM-398. Figures 10A and 10B depict line graphs demonstrating the toxicities associated with MM-398 and oxaliplatin given as monotherapy or combined therapy given concurrently (A) or staggered, with oxaliplatin given 1 day after MM-398 administration (B). Co-administration of MM-398 and oxaliplatin leads to significant toxicities as measured by loss of body weight, whereas delaying oxaliplatin administration by 24h after MM-398 does not lead to significant changes in body weight.

Figure 11A-11F are bar graphs depicting hematological and liver toxicities following treatment with MM-398 with or without oxaliplatin given either concurrently or sequentially with MM-398. Hematological toxicities (A-C) were improved by delayed

administration of oxaliplatin. Liver enzymes (D-F) remained comparable to monotherapies when oxaliplatin administration was delayed.

These preclinical findings support the therapeutic use of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2). Figure 12 depicts a graphical representation of the study design employing the combination of MM-398 + 5-FU/LV + oxaliplatin in (Arm 1) and MM-398 + 5-FU/LV (Arm 2), and nab-paclitaxel + gemcitabine (Arm 3) as described herein.

For example, use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of: (a) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (b) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (c) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (d) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient, wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (e) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the

oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; (f) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; or (g) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2-85mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan. Each of these exemplary uses can be modified to replace the doses of liposomal irinotecan, oxaliplatin, leucovorin and 5-flurouracil disclosed herein in the following passages relating to these specific components. Sometimes the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes. Sometimes, the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

As provided herein, irinotecan can be administered in an irinotecan liposome preparation. Preferably, the liposomal irinotecan is irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"), the formulation referred to herein as "MM-398" (also known as PEP02, see US 8,147,867) is a form of "nanoliposomal irinotecan" (also called "irinotecan liposome" or "liposomal Irinotecan"). MM-398 is irinotecan as the irinotecan sucrose octasulfate salt encapsulated in a nanoliposome drug delivery system.

The liposomal irinotecan can be a pharmaceutical composition prepared for human intravenous administration. For example, the liposomal irinotecan may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of

liposomal irinotecan may be diluted, e.g., in 500 mL of 5% dextrose injection USP, to provide a variety of concentrations, for example, 5 mg/mL, and may be infused over a 90 minute period.

The active ingredient of the MM-398 injection, irinotecan, is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38. SN-38 is cleared via glucuronidation, (for which major pharmacogenetic differences have been shown), and biliary excretion. These drug properties contribute to the marked differences in efficacy and toxicity observed in clinical studies with irinotecan.

The liposomal irinotecan can be a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space that contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for every 200 phospholipid molecules.

The amount of liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 180 mg/m^2, preferably 60 mg/m^2 when administered in combination with oxaliplatin and 5-fluorouracil for treatment of pancreatic cancer (dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt). The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received MM-398, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m^2 (amount of irinotecan base, equivalent to 60 -180 mg/m^2 dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt) and 353 patients with cancer using population pharmacokinetic analysis. Over the dose range of 50 to 155 mg/m^2, the C_{max} and AUC of total irinotecan increases with dose. Additionally, the

C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

The combination treatment described herein encompasses administration of MM-398 liposomal irinotecan in combination with multiple additional active agents: oxaliplatin, leucovorin and 5-fluorouracil, in doses and schedules to human patients with metastatic pancreatic cancer not previously treated with a prior chemotherapeutic agent in the metastatic setting as described herein.

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis. An exemplary effective amount of 5-fluorouracil administered to a human patient can range from about 2,000 mg/m^2 to about 3,000 mg/m^2. In some embodiments, the amount of 5-fluorouracil administered to the human patient is 2,400 mg/m^2.

Leucovorin is optionally administered prior to the 5-fluorouracil. Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase. Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levo-leucovorin") has also been approved by the FDA for treatment of cancer. The dosage of leucovorin is that of the racemic mixture containing both dextro (d) and levo (l) isomers, or optionally the (l) form of leucovorin at half the dosage of the (l + d) racemic form. An exemplary effective amount of leucovorin administered to the human patient can include an amount of (l)-form leucovorin ranging from about 100 mg/m^2 to about 300 mg/m^2. In some embodiments, the amount of (l)-form leucovorin administered to the human patient is 200 mg/m^2. In other embodiments, the leucovorin administered is the

(l + d)-form of leucovorin, in an amount ranging from about 200 mg/m^2 to about 600 mg/m^2. In some embodiments, the amount of (l + d)-form of leucovorin administered is 400 mg/m^2.

Oxaliplatin is a platinum-based drug that acts as a DNA cross-linking agent to effectively inhibit DNA replication and transcription, resulting in cytotoxicity which is cell-cycle non-specific. Oxaliplatin is typically used in combination with infusional 5-FU/LV, and is approved for use in advanced colorectal cancer (refer to package insert for more details). The effective amount of oxaliplatin administered to the human patient can range from about 30 mg/m^2 to about 150 mg/m^2, for example, from about 40 mg/m^2 to about 100 mg/m^2, or an amount of oxaliplatin of 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, or 95 mg/m^2.

Dose modifications may be made to methods of administering the combination treatment described herein as a result of adverse events, include hematological and non-hematological adverse events.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of MM-398 administered according to the embodiments herein. In some embodiments, the dose of MM-398 is modified according to Table 1.

Table 1A: Examples of Dose Modifications for MM-398 (salt)

Toxicity NCI CTCAE v4.0	Occurrence	MM-398 adjustment in patients receiving 60 mg/m²‡ (salt)	Patients homozygous for UGT1A1*28 without previous increase to 60 mg/m² (salt)
Grade 3 or 4 adverse reactions	Withhold MM-398. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1 or baseline grade resume MM-398 at:		
	First	45 mg/m²	35 mg/m²
	Second	35 mg/m²	30 mg/m²
	Third	Discontinue MM-398	Discontinue MM-398
Interstitial Lung Disease	First	Discontinue MM-398	Discontinue MM-398
Anaphylactic Reaction	First	Discontinue MM-398	Discontinue MM-398

In some embodiments, the first, second or any subsequent dose of MM-398 can be reduced by 20-30% (including dose reductions of 20%, 25% and/or 30%) in response to patient tolerability considerations such as an adverse reaction to a first or subsequent dose of MM-398 and/or other antineoplastic agent, and/or identifying a patient as being homozygous for the UGT1A1*28 allele. In some embodiments, the second or subsequent dose of MM-398 is reduced by about 20%, 25% or 30% (e.g., a dose reduction from 60 mg/m2 to . In some embodiments, the dose of MM-398 is reduced by 25%. In some embodiments, the dose of

MM-398 is reduced by 30%. In some embodiments, the reduced dose of MM-398 is in a range starting from 30 mg/m^2 to (and including) 55 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 60 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 45 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 35 mg/m^2.

Other dose reduction schedules are provided Tables 1B-1E below. When the starting (initial) dose of MM-398 is 60 mg/m^2, 5FU 2400mg/m^2, LV(l+d) 400mg/m^2 and Oxaliplatin is either 85mg/m2 OR 60mg/m2, then the first dose reduction in response to a grade III or IV hematotoxicity is preferably a 25% dose reduction for each of the MM-398, 5-FU and Oxaliplatin doses for each administration of the antineoplastic therapy. For persistent toxicities despite the first dose reduction, an additional 25% dose reduction in each of the antineoplastic agents of MM-398, 5-fluorouracil and oxaliplatin is preferred. Further toxicity will then lead to discontinuation of treatment in some instances. For non-hematologic toxicities, the same dose reduction schema can be followed as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which can be selected based on the medically appropriate dose for the patient.

Table 1B Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	1800
Second Reduction	35	35	1350

Table 1C Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	1800
Second Reduction	35	45	1350

Table 1D Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	2400
Second Reduction	35	35	1800

Table 1E Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	2400
Second Reduction	35	45	1800

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of Oxaliplatin administered according to the embodiments herein. In some embodiments, the dose of Oxaliplatin is reduced by 20-30%. In some embodiments, the, the dose of Oxaliplatin is reduced by 20%. In some embodiments, the, the dose of Oxaliplatin is reduced by 25%. In some embodiments, the, the dose of Oxaliplatin is reduced by 30%. In some embodiments, the reduced dose of Oxaliplatin is in a range from 30 mg/m^2 to 75 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 75 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 65 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 60 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 34 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of 5-fluorouracil administered according to the embodiments herein. In some embodiments, the dose of 5-fluorouracil is reduced by 20-30%. In some embodiments,

the, the dose of 5-fluorouracil is reduced by 20%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 25%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 30%. In some embodiments, the reduced dose of 5-fluorouracil is in a range from 1000 mg/m^2 to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1350 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1200 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include further reducing or otherwise modifying the dose of MM-398, Oxaliplatin and/or 5-fluorouracil administered according to the embodiments herein.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of more than one of MM-398, Oxaliplatin and 5-fluorouracil administered according to the embodiments herein.

Additional dose modifications for MM-398, Oxaliplatin and/or 5-fluorouracil can be found in the respective Package Inserts, which are incorporated herein by reference.

In one embodiment, the method of administering the combination treatment comprises 34, 45, or 60 mg/m^2 of liposomal irinotecan, 34, 42, 45, 60 or 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 1,200, 1,350, 1,800 or 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Thus, in some embodiments, the method of administering the combination treatment to treat the metastatic adenocarcinoma of the pancreas in the human patient comprises:

(A) (i) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and

2,400mg/m^2 5-FU; (v) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (B) (i) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2

oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; or (C) (i) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi)

60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or(xx) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU.

Liposomal irinotecan is preferably administered intravenously, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin. In one embodiment, liposomal irinotecan is administered prior to oxaliplatin, 5-FU and leucovorin. In another embodiment, leucovorin is administered prior to 5-FU. In another embodiment, the MM-398 liposomal irinotecan is administered followed by administration of the oxaliplatin, followed by administration of the leucovorin, and followed by the administration of the 5-fluorouracil. In certain embodiments, the liposomal irinotecan is administered to the patient intravenously over 90

minutes. In another embodiment, the oxaliplatin is administered to the patient intravenously over 120 minutes. In another embodiment, 5-FU is administered intravenously over 46 hours. In one embodiment, the oxaliplatin is administered from about 6 to about 72 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered for example, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, or 72 hours, after administration of the liposomal irinotecan. In another embodiment, leucovorin is administered intravenously over 30 minutes. In various embodiments the liposomal irinotecan is MM-398. In various embodiments, the human patient with metastatic pancreatic cancer is pre-medicated with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan, and other active agents.

Further embodiments of the invention

The following methods and embodiments can be considered alone, in combination other embodiments in this section, or in combination with the methods disclosed above. The invention provides methods for treating pancreatic cancer in a human patient, such as in a patient not previously treated with a chemotherapeutic agent in the metastatic setting, the method comprising administering to the patient liposomal irinotecan, also referred to as MM-398 (e.g., irinotecan sucrose octasulfate salt liposome injection) in combination with oxaliplatin, leucovorin and 5-FU.

1. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

2. The method of embodiment 1, wherein the amount of MM-398 liposomal irinotecan administered is administered is 60 mg/m^2 or 80 mg/m^2.

3. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to

the subject 60 mg/m^2 of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

4. The method of any one of embodiments 1-3, wherein the amount of oxaliplatin administered is from about 50 mg/m^2 to about 100 mg/m^2, such as about 60 mg/m^2 to about 85 mg/m^2, for example 60 mg/m^2, 75 mg/m^2, or 85 mg/m^2.

5. The method of any one of embodiments 1-4, wherein the leucovorin administered at a dosage of 400 mg/m^2 of the (l + d) racemic form, or 200 mg/m^2 of the (l) form.

6. The method of any one of embodiments 1-5, wherein the amount of 5-FU administered is 2,400 mg/m^2.

7. The method of any one of embodiments 1-6, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU are administered at least once, such as wherein the MM-398, oxaliplatin, leucovorin, and 5-FU are administered on days 1 and 15 of a 28-day cycle.

8. The method of any one of embodiments 1-7, wherein multiple cycles are administered.

9. The method of any one of embodiments 1-8, wherein the pancreatic cancer is adenocarcinoma of the pancreas, such as unresectable, locally advanced or metastatic adenocarcinoma of the pancreas, for example, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas; or wherein the metastatic pancreatic cancer is an exocrine metastatic pancreatic cancer selected from the group consisting of Duct cell carcinoma, Acinar cell carcinoma, Adenosquamous carcinoma, Cyst adenocarcinoma (serous and mucinous types), Giant cell carcinoma, Invasive adenocarcinoma associated with cystic mucinous neoplasm or intraductal papillary mucinous neoplasm, Mixed type (ductal-endocrine or acinar-endocrine), Mucinous carcinoma, Pancreatoblastoma, Papillary-cystic neoplasm (Frantz tumor), Papillary mucinous carcinoma, Signet ring carcinoma, Small cell carcinoma, Unclassified, Undifferentiated carcinoma, serous cystadenocarcinoma, and Solid and Pseudopapillary tumors.

11. The method of any one of embodiments 1-10, wherein the oxaliplatin is administered to the patient prior to the leucovorin, such as wherein the leucovorin is administered to the patient prior to the 5-FU, optionally wherein the MM-398 liposomal irinotecan is administered to the patient prior to the oxaliplatin, leucovorin, and 5-FU.

12. The method of embodiment 11, wherein the MM-398 is administered over 90 minutes, followed by administration of the oxaliplatin over 120 minutes, followed by administration of the leucovorin over 30 minutes, followed by the administration of the 5-FU over 46 hours.

In a particular embodiment, a human patient with metastatic adenocarcinoma of the pancreas who has not previously been treated with any chemotherapeutic agent in the metastatic setting, is treated with a combination regimen of the present disclosure, the method comprising, intravenously administering to the patient, beginning on day 1 of a 2-week cycle, 80 mg/m^2 of MM-398 liposomal irinotecan over 90 minutes, followed by 60-85 mg/m^2 oxaliplatin, followed by 200 mg/m^2 of the *(l)* form of leucovorin, or 400 mg/m^2 of the *(l+d)* racemic form of leucovorin, followed by 2,400 mg/m^2 5-FU, wherein the human patient is treated with one or multiple cycles. In the embodiments disclosed herein, the effective amount of MM-398 liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 80 mg/m^2. In various embodiments, the amount of MM-398 liposomal irinotecan administered to the human patient is 60 mg/m^2 or 80 mg/m^2. In the embodiments disclosed herein, the effective amount of Oxalyplatin administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 85 mg/m^2. In various embodiments, the amount Oxalyplatin administered to the human patient is 60 mg/m^2 or 85 mg/m^2. In one variant of this embodiment, oxaliplatin is administered over 120 minutes, leucovorin is administered over 30 minutes, and 5-FU is administered over 46 hours.

Examples

Example 1: *In vitro* pancreatic cancer cell exposure to topoisomerase 1 inhibitor

Simulated tumor exposure of SN-38 in patients administered with free irinotecan or MM-398 were shown in Figure 1A. MM-398 is shown to result in prolonged SN-38 duration in tumors compared to free irinotecan (CPT-11). The effect of various SN-38 durations on cell growth inhibition was studied in a panel of pancreatic cell lines (AsPC-1, BxPC-3, Capan-2, CFPAC-1, and MiaPaCa-2). Figure 1B illustrates the in vitro conditions for mimicking this clinically comparable SN-38 exposure of the 2 drugs, where cells exposed to SN-38 at high concentrations for a short period of time approximates for free irinotecan, and at low concentrations for a long period of time for MM-398. The results and experimental conditions are summarized in Figure 1C. For example, cells incubated with 139 nM of SN-38 for 144h vs. 417 nM for 24h have similar SN-38 tumor exposure ratios of MM-398 vs. free

irinotecan in patient tumors. Under these clinically relevant conditions, prolonged exposure (i.e. MM-398) primarily resulted in more pancreatic cancer cell growth inhibition compared to short exposure at high concentrations (i.e. free irinotecan). Similar results were also obtained when SN-38 were combined with 5-FU or oxaliplatin, demonstrating that prolonged exposure also led to increased cell growth inhibition when combined with these other chemotherapeutics agents that are used in the FOLFIRINOX regimen.

Example 2: Evaluation of *in vivo* tolerability and efficacy of combination therapies in an animal model

BxPC-3 and CFPAC-1 mouse xenograft studies (efficacy):

Tissue culture: BxPC-3 cells were cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin. CFPAC-1 cells were also cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin.

Animals: Experiments were performed according to approved guidelines. Female NOD.scid mice were obtained from Charles River Laboratories (Wilmington, MA). BxPC-3 or CFPAC-1 cells were inoculated into the right hind flank at 5e6 cells in a total volume of 50 uL per mouse. Eight animals were treated per group, unless otherwise indicated. Animals were randomized and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 2 weeks post post-final dose.

PDX19015 mouse xenograft study (efficacy and tolerability):

Animals: Experiments were performed according to approved guidelines. Female CB.17 SCID mice were obtained from Roswell Park Cancer Institute (Buffalo, NY), initially at 6-8 weeks of age. Per treatment group, 8 animals were treated, unless otherwise indicated. Tumor pieces were derived from donor mice and engrafted subcutaneously. Animals were randomized

and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured twice weekly during the dosing cycle, then once weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 100 days post-first dose. Tolerability: Mouse weights were measured once weekly to monitor treatment tolerability. Mice were euthanized when body weight declined to ≥20% below baseline, or they exhibited overt signs of poor general health.

Delayed dosing of oxaliplatin:

Animals: Experiments were performed according to approved guidelines. Female CD-1 mice were obtained from Charles River Laboratories (Wilmington, MA). Tolerability studies were performed in naïve (non-tumor-bearing) mice. Three animals were treated per group.

Treatment tolerability: Agents were administered intravenously at their pre-defined maximum tolerated doses (MM-398, 50mg/kg; oxaliplatin, 17mg/kg). Each drug was administered individually, or in combination. Combinations were given in one of 3 independent dosing schedules: coinjection (drugs administered simultaneously), MM-398 given on day 1 and oxaliplatin given on day 2 (24h delay), or MM-398 given on day 1 and oxaliplatin given on day 4 (72h delay). A single administration of each drug was given. Mouse body weights were measured daily for up to 2 weeks post-treatment. Mice were euthanized when body weight declined to ≥20% below baseline, they exhibited overt signs of poor general health, or at 2 weeks post-treatment (end of study).

Measurement of hematologic and liver toxicities: At the end of study, terminal bleeds were performed for each mouse via cardiac puncture. Hematologic function (blood cell count) was measured by Hemavet (Drew Scientific, Miami Lakes, FL), according to manufacturer's protocol. Liver function (enzyme levels) was measured by CatalystDx (Idexx Laboratories, Westbrook, ME) according to the manufacturer's protocol.

Example 3: Treatment of Pancreatic Cancer

As schematically shown in Figure 12, the present study is an open-label, phase 2 comparative study to assess the safety, tolerability, and efficacy of MM-398 in combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with metastatic pancreatic adenocarcinoma who have not received prior chemotherapy. This study assesses the following regimens: (1) MM-398 + 5-FU/LV + oxaliplatin (Arm 1), (2) MM-398 + 5-FU/LV (Arm 2) and (3) nab-paclitaxel + gemcitabine (Arm 3).

This phase 2 study evaluates the preliminary safety and efficacy of MM-398 + 5-FU/LV with or without oxaliplatin versus nab-paclitaxel + gemcitabine in patients with previously untreated mPAC. The study may also provide important information on the impact of MM-398 combination treatment on patient HRQL and identify potential biomarkers of response.

In the study, MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen. The addition of oxaliplatin to the NAPOLI-1 regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398 prolonged PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the efficacy of FOLFIRINOX.

A modified triplet combination regimen of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU)/leucovorin is provided herein, whereby no bolus of 5-FU will be administered. The target dose of oxaliplatin (60-85 mg/m^2) is evaluated in the Arm 1 combination regimen with the continuous infusion dose of 5-FU (excluding the bolus), and the every 2 week dose of MM-398 previously shown to be tolerable and efficacious in combination with 5-FU. Note that with MM-398 dosing, the C_{max} of SN-38 is expected to be lower than would be expected for standard dosing with free irinotecan.

The study is conducted in two parts, as illustrated in the schematic of Figure 12: 1) a safety run-in of the MM-398 + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the MM-398 + 5-FU/LV + oxaliplatin regimen, the MM-398 + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), and a nab-paclitaxel + gemcitabine control arm.

Part 1:

Part 1 consists of an open-label safety run-in of the combination regimen in Arm 1: MM-398 + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and MM-398 + 5-FU/LV has been demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore was not included in this part of the study. The safety run-in enrolls small cohorts of patients following a traditional 3 + 3 dose escalation design in order to confirm the target dose of oxaliplatin. Dose limiting toxicities (DLTs) are evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2^{nd} dose of study treatment if there is a treatment delay in cohorts of patients to determine if the target combination dose is tolerable (note: the target combination dose is based on the established dose of the FOLFIRINOX regimen)). If there are no DLTs within the safety evaluation period, then the subsequent cohort is initiated following agreement between the Investigators, Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort is expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose is considered to exceed the safety and tolerability criteria of the combination, and the dose is not be escalated further; however, lower doses can be explored. The Part 2 dose is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Additionally, UGT1A1*28 allele status is considered when evaluating DLTs. Based on previous experience with irinotecan, individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan, in a study of 66 patients who received single-agent irinotecan (350 mg/m^2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. Importantly, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of accompanying life threatening neutropenia is described (for details refer to the prescribing information for irinotecan). Population PK studies of MM-398 have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study, no differences in toxicity were seen in

cohorts of heterozygous or WT patients, and DLTs of diarrhea with or without accompanying dehydration or fatigue, were seen in both cohorts. For these reasons, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results are not required prior to the first dose of MM-398 on this study and the starting dose for all patients will be 80 mg/m^2. However, if patients are known to be homozygous for UGT1A1*28, the dose of MM-398 may be reduced as described herein.

Part 2:

Part 2 consists of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either MM-398 + 5-FU/LV + oxaliplatin, MM-398 + 5-FU/LV, or nab-paclitaxel + gemcitabine. The randomization is stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1).

The following adverse events are common (≥ 40%) with past oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the MM-398-containing combination regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. Additional adverse events may be anticipated, as described in the package insert for oxaliplatin, including allergic and anaphylactic reactions. In a Phase 3 study of the FOLFIRINOX combination, the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia. Considering these expected toxicities, Arm 1 is evaluated for safety and tolerability in Part 1 of the study as described below.

A dose of oxaliplatin of 85 mg/m^2 is the target dose for Part 2 of this study. The purpose of Part 1 is to confirm whether this dose is compatible when MM-398 is used instead of conventional irinotecan. In case there are any unexpected toxicities, 3 to 6 patients are initially treated at a lower dose of oxaliplatin (60 mg/m^2, see Table 1) prior to administration of oxaliplatin at the highest proposed dose of 85 mg/m^2. The dose of the triplet combination to be administered in Part 2 of the study is defined as the highest dose level at which a DLT is experienced by fewer than 2 patients in a cohort of 3 to 6 patients. If one patient experiences a treatment-related toxicity that qualifies as a DLT, up to 3 additional

patients are enrolled at that dose level, for no more than 6 total patients per cohort. If no additional DLTs are observed, the dose escalation resumes. If a second patient experiences a treatment-related toxicity that qualifies as a DLT at that dose, that dose is considered to exceed the optimal safety and tolerability criteria of the combination. The dose to be used in Part 2 is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Dosing of patient cohorts begins at dose level -1 with planned escalation to dose level -2B (target dose), in which the dose for one of the three drugs is increased while the other two drugs will maintain a constant dose. If the -1 dose level is evaluated and deemed to be safe, escalation to the -2B dose level may be initiated. Any decisions to de-escalate, as well as enrollment at alternative doses following de-escalation, must be made according to the established decision process for dose escalation, as described herein. Planned dose escalation for the Arm 1 combination regimen is outlined in Table 2 below; additional details on dose administration as described herein in the section "Study Treatment".

Table 2 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Arm 1: MM-398 + 5-FU/LV + Oxaliplatin

The order of the infusions to be administered in the clinic is as follows: MM-398 administered first, followed by oxaliplatin, then LV, followed by 5-FU.

In Part 1, patients receive the oxaliplatin infusion 2 hours after the completion of the MM-398 infusion. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly

after completion of the MM-398 infusion. If any grade 3 or higher infusion reactions are seen in Part 2 patients, the DSMB may elect to revert back to administration of oxaliplatin two hours after the completion of the MM-398 infusion.

Arm 1 Premedication

All patients must be premedicated prior to MM-398 infusion, 5-FU/LV infusion, and oxaliplatin infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan, 5-FU, and oxaliplatin administration, or the Summary of Product Characteristics (SmPC) for sites located in the European Union (EU). Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

Arm 2: MM-398 + 5-FU/LV

The order of the infusions to be administered in the clinic will be as follows: MM-398 will be administered first, followed by LV, followed by 5-FU.

Arm 2 Premedication

All patients must be premedicated prior to MM-398 infusion and 5-FU/LV infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan and 5-FU administration, or the SmPC for sites located in the EU. Atropine may be prescribed prophylactically, according to standard institutional practices, for patients who experienced acute cholinergic symptoms in the previous cycles.

Doses and Administration of MM-398 (Arms 1 and 2)

MM-398 is administered by intravenous (IV) infusion over 90 minutes (±10 minutes) every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) or normal saline to a final volume of 500 mL. Care should be taken not to use in-line filters or any diluents other than D5W or normal saline. MM-398 can be administered at a rate of up to 1 mL/sec (30 mg/sec).

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

Doses and Administration of 5-FU and Leucovorin (Arms 1 and 2)

Leucovorin is administered at a dose of 400 mg/m^2 of the (l + d)- racemic form, or (l) form 200 mg/m^2, as an IV infusion over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle

5-FU is administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle

Leucovorin should be reconstituted per the instructions on the package insert, SmPC or standard institutional guidelines for reconstitution of leucovorin.

Leucovorin should be administered prior to the 5-FU infusion (on Arm 1, leucovorin will be given concurrently with oxaliplatin). Actual dose of 5-FU and leucovorin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

Doses and Administration of Oxaliplatin (Arm 1 only)

In Part 1, oxaliplatin is administered at increasing dose levels as indicated in Table 2 (from 60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle

In Part 2, oxaliplatin is administered at a dose of 85 mg/m^2, IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle (if target dose is confirmed in accordance with methods described herein).

Oxaliplatin should be prepared according to the instructions on the package insert, SmPC or per standard institutional guidelines for preparation and administration of oxaliplatin.

Oxaliplatin should be administered following MM-398 infusion; in Part 1, the first 3 patients in Dose Level 1 begin the oxaliplatin infusion two hours after the completion of the MM-398 infusion. Actual dose of oxaliplatin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose is allowed for ease of dose administration.

Arm 3: nab-Paclitaxel + Gemcitabine

The order of the infusions to be administered in the clinic is as follows: nab-paclitaxel will be administered first, followed by gemcitabine.

Arm 3 Premedication

All patients receiving nab-paclitaxel and gemcitabine should be pre-medicated per the respective package inserts. If different institutional guidelines exist for premedication of weekly nab-paclitaxel and/or gemcitabine, the investigator should use their standard practice or the SmPC for sites located in the EU.

Doses and Administration of nab-Paclitaxel and Gemcitabine (Arm 3)

The nab-paclitaxel will be administered at 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

The gemcitabine will be administered at 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

Dose Limiting Toxicities (DLTs)

For MM-398 administered in combination with 5-FU/LV and oxaliplatin, the following adverse events are considered as dose limiting toxicities (DLTs) if they occur during the first cycle of treatment and are deemed related to the study treatment regimen:

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia);
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection;

- Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity; and
- Any grade 4 non-hematologic toxicity with the specific exclusion of: Fatigue/asthenia < 2 weeks in duration, increases in alkaline phosphatase level, nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen), and diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

Any toxicity that is related to disease progression will not be considered a DLT.

The safety assessment period for purposes of DLT evaluation and dose escalation decisions is one cycle of treatment (i.e. 28 days; or 14 days after the 2nd dose of study treatment if there is a treatment delay according as described herein). The dose can escalate to the next level only after the safety data have been evaluated at the current dose level (once the last patient enrolled in the cohort completes the first cycle of treatment) and the criteria for safety and tolerability of the optimal dose have not been exceeded (see Section Part 2 dose definition). In addition, any drug-related toxicities of Grade 3 or higher that arise after Cycle 1 (if applicable) are assessed for their potential relationship to cumulative MM-398 or combination therapy doses and considered in the decision to escalate the dose. PK data may be available, but is not be required for decisions on dose escalation.

Inclusion Criteria	Exclusion Criteria

In order for inclusion into the study, patients must have/be:
• Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting
  ○ Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment
  ○ Part 2: must have
	Patients must meet all the inclusion criteria and none of the following exclusion criteria:
	• Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed)
	• Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy)
	• Known metastasis to the central nervous system
	• Clinically significant gastrointestinal disorder including hepatic disorders, bleeding,

Inclusion Criteria	Exclusion Criteria
metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed • Measurable or non-measurable disease as defined by RECIST v1.1 • ECOG performance status of 0 or 1 • Adequate biological parameters as evidenced by the following blood counts: o ANC > 1,500 cells/μl without the use of hematopoietic growth factors, o Platelet count > 100,000 cells/μl, and o Hemoglobin > 9 g/dL • Adequate hepatic function as evidenced by: o Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and o AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) • Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.72 m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean	inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction • History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. • Known hypersensitivity to any of the components of MM-398, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin • Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only) • Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: o Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion o NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure o Known historical or active infection with HIV, hepatitis B, or hepatitis C • Active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome • Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan • Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin • Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only) • Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or

Inclusion Criteria	Exclusion Criteria
body weight should be used instead. • Normal ECG or ECG without any clinically significant findings • Recovered from the effects of any prior surgery or radiotherapy • ≥ 18 years of age • Agreeable to submit unstained archived tumor tissue for analysis, if available • Able to understand and sign an informed consent (or have a legal representative who is able to do so)	interfere with the interpretation of the results • Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 3 months following the last dose of study drug.

Dose Modifications

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03). All dose reductions for all arms should be based on the worst preceding toxicity.

Dosing may be held for up to 2 weeks from when it was due to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than 2 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor regarding risks and benefits of continuation. If oxaliplatin is not well tolerated in patients enrolled in Arm 1, oxaliplatin may be discontinued and patients may continue to receive MM-398 + 5-FU/LV at the discretion of the Investigator.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Dose Modifications

Prior to each dosing, patients must have: ANC ≥ 1500/mm^3, WBC ≥ 3500/ mm^3, Platelet count ≥ 100,000/mm^3 and Diarrhea ≤ Grade 1.

Treatment should be delayed to allow sufficient time for recovery to levels noted above, and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to ≥ 1500/mm^3 and the patient must have recovered from infection. For Grade 3 or 4 non-hematological toxicities, treatment should be delayed until they resolve to Grade 1 or baseline. Guidelines for dose adjustments of each individual treatment within the regimen are found in the tables below for Arm 1 (Table 3), and for Arm 2 (Tables 6 through 14). In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management should be followed.

For all tables below, patient should be withdrawn from study treatment if more than 2 dose reductions are required or if MM-398 reductions lower than 35 mg/m^2 are required. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well.

Treatment discontinuation that is required due to MM-398 or 5-FU toxicity will result in discontinuation from the study. However, for Arm 1, toxicity that requires discontinuation from oxaliplatin only (e.g. neuropathy) will result in the option to continue on study treatment with MM-398 + 5-FU/LV only for all future dosing.

<u>Arm 1 Dose Modifications</u>

The starting dose of ONIVYDE will be 60mg/m^2, 5FU 2400mg/m^2, LV 400mg/m^2 and Oxaliplatin either 85mg/m^2 or 60mg/ m^2. Dose reduction will be 25% reduction in all agents for any grade III-IV Hematotoxicity. For persistent toxicities despite the first dose reduction, and additional 25% dose reduction in all agents will occur. Further toxicity will then lead to discontinuation from trial.

For non-hematologic toxicities, the dose reduction will be the same dose reduction schema as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which will be as shown in Table 3.

Table 3: Arm 1 Dose Modifications

Worst Toxicity by CTCAE Grade	**MM-398**	**5-FU**	**Oxaliplatin**
Hematological Toxicities			
Grade 2 neutropenia (ANC <1500 - 1000 cells/ mm^3)	100 % of previous dose	100 % of previous dose	1st occurrence: 100% of previous dose
Grade 3 or 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia[a]	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/$m^2$2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
≥ Grade 2 thrombocytopenia (Grade 2: platelets ≤ 75,000/mm^3 – 50,000/mm^3 OR Grade 3-4: platelets < 50,000/mm^3)	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2

Other hematologic toxicities not specifically listed above	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[b]			
Grade 1 or 2, including diarrhea[c]	100 % of previous dose	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100 % of previous dose
Grade 3 or 4, including diarrhea[d] (except nausea and vomiting)	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% *except for Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2

Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Optimize anti-emetic therapy AND reduce dose by 25% ; if the patient is already receiving a reduced dose, reduce dose an additional 25%	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Grade 2 hand foot syndrome	100 % of previous dose[d]	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	100 % of previous dose
Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Discontinue therapy	No dose modifications required
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	No dose modifications required[e]	Discontinue therapy	No dose modifications required

Sensory neuropathy	No dose modifications required[e]	No dose modifications required[e]	Grade 2, persistent: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, recovers prior to next cycle: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, persistent: Discontinue therapy Grade 4: Discontinue therapy

[a]Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia.

[b]Asthenia and Grade 3 Anorexia do not require dose modification

[c]Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment

[d] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment

Arm 2 Dose Modifications

Dosing may be held for up to 3 weeks from when it was due, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any

patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Table 4

Grade 1: Transient flushing or rash, drug fever <38º C (<100.4º F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Table 5

Grade 1 • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2 • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 25-50 mg IV
Grade 3 • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary

• No further treatment with MM-398 will be permitted
Grade 4 • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table 6: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm^3 (Worst CTCAE grade)	**MM-398 Dose for Next Cycle**		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28** **Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
$\geq$ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose

< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 7: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below. Infusion reactions should be handled as described above.

Table 8: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
Grade 1 or 2 (2-3 stools/day >	100% of previous dose	100% of previous dose	100% of previous dose

pretreatment or 4-6 stools/day > pretreatment)			
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 9: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia

Worst Toxicity CTCAE Grade	**MM-398 Dose for Next Cycle**		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2

5-FU and Leucovorin Dose Modifications

Guidelines for 5-FU dose modifications are provided below. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for MM-398 infusion reaction management should be used.

5-FU Dose Modifications for Hematological Toxicities

Prior to the next dose in a cycle or prior to initiating a new cycle of therapy, the patients must have:

- ANC ≥ 1500/mm^3
- WBC ≥ 3500/mm^3
- Platelet count ≥ 75,000/mm^3 (according to the European summary of product characteristics for 5-FU, the platelets should have recovered to ≥ 100,000/mm^3 prior to initiating therapy)

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines provided in the table below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 10: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC (cells/mm^3)		Platelets (cells/mm^3)	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25%[b]	Reduce dose by 25% [b]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study

5-FU Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until all Grade 3 or 4 non-hematological toxicities resolve to Grade 1 or baseline. Guidelines for dose adjustment of 5-FU related toxicities are provided below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 11: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[c]

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25%[b]	Reduce dose by 25%[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25%[b], except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25%[b],except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study
[c] Asthenia and Grade 3 Anorexia do not require dose modification

*MM-398 Dose Modifications for UGT1A1*28 Positive Patients (Arms 1 and 2)*

Patients are tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of MM-398. All patients will begin dosing at 80 mg/m^2 (salt), however future doses may be reduced for patients who are positive (i.e. homozygous) for UGT1A1*28 7/7 genotype. For Part 1 patients receiving 80 mg/m^2 (salt) of MM-398: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m^2 (salt) after discussion between the PI, Sponsor and Medical Monitor. Any Part 1 patients who receive a reduced dose during Cycle 1 due to UGT1A1*28 homozygosity will not be evaluable for the cohort and are replaced.

Arm 3 Dose Modifications

Dose level reductions required due to toxicities related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 12.

Table 12: Dose Level Reductions for nab-Paclitaxel and Gemcitabine

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800

2nd dose reduction	75	600
If additional dose reductions required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 13 and adjustments related to other toxicities are provided in Table 14.

Table 13: nab-Paclitaxel and Gemcitabine Dose Modifications at the Start of Each Cycle or Within a Cycle for Neutropenia and/or Thrombocytopenia.

Cycle Day	**ANC (cells/mm³)**		**Platelet count (cells/mm³)**	**Nab-paclitaxel / Gemcitabine**
Day 1	<1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = absolute neutrophil count

Table 14: nab-Paclitaxel and Gemcitabine Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	**Nab-paclitaxel**	**Gemcitabine**
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves ≤ Grade 1; resume at next dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next dose level	

Disease Evaluation

Tumor responses are evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, to establish disease progression by CT or MRI. In addition, other imaging procedures, as deemed appropriate by the Investigator, are performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Investigators should select target and non-target lesions in

accordance with RECIST v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

Tumor assessments should be completed until it has been determined that the patient has progressive disease (in accordance with RECIST v1.1). For patients who do not have documented disease progression per RECIST v. 1.1 at the time of treatment termination, imaging studies should be continually performed into the follow-up period every 8 weeks until disease progression is documented. Continued imaging follow-up on schedule is recommended to reduce potential bias in the evaluations of the impacts of the experimental treatments on disease.

EORTC-QLQ-C30 and EQ-5D-5L (Part 2 Only)

Health-related quality of life (HRQL) is assessed by the EORTC-QLQ-C30 and EQ-5D-5L instruments. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. EQ-5D is a generic, preference-based measurement of HRQL. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to do.

Patients are required to complete both questionnaires at time points outlined in the Schedule of Assessments. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients for whom validated translations of the questionnaires are available will be required to complete the questionnaire.

Efficacy Analysis

In the assessments of efficacy, each MM-398-containing arm is compared to the control arm. Efficacy comparisons use stratified analyses, incorporating randomization strata. Each comparison uses 0.10 level one-sided testing to evaluate whether the MM-398 -containing

arm improves the efficacy parameter. Confidence intervals are presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals are not adjusted for multiple comparisons. The primary efficacy comparisons are based on the ITT population, which includes all randomized patients.

Tumor evaluation is measured according to RECIST v1.1. For each patient, progression free survival time is determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical Progression of Disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time is censored at the time of the last non-PD tumor assessment.

A primary analysis is conducted when the Week 24 progression-free status for all randomized patients can be determined, anticipated at approximately 24 weeks after the last patient is randomized. A subsequent analysis for PFS and other endpoints is performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients.

Primary Efficacy Analysis

In the intention-to-treat (ITT) analysis, a patient is considered to have achieved progression-free survival at 24 weeks if the patient has data to indicate the patient has not progressed at 24 weeks. That is, a patient is considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.

Patients who do not meet the 24-week progression-free achievement criteria (e.g. patients progressed/died up to Week 24, patients censored prior to Week 24), if progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment.

For each arm, the progression-free survival achievement rate at 24 weeks is estimated by the number of patients meeting the 24 week achievement criteria divided by the number of ITT patients in the arm. The rate estimates are presented with corresponding 95% confidence intervals. Each MM-398 containing arm is assessed for increase in rate relative to

the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at 0.10 level of significance.

Secondary Efficacy Analyses

Progression-Free Survival (PFS) is descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits are presented. For each MM-398-containing arm, PFS is compared to the control arm. Hypothesis tests are conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment are considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI are calculated for each treatment arm. For each MM-398-containing arm, ORR is compared to the control arm. Differences in objective response rate between each MM-398-containing arm and control arm are provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, are used to compare objective response rates.

The maximum reduction (% change from baseline) in CA19-9 is computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses is carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement is considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline are included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response is estimated, along with corresponding 95% confidence intervals, by treatment arm.

Overall Survival (OS) is the time from randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS is descriptively summarized for each arm using Kaplan-Meier

methodology. For each MM-398-containing arm, OS is compared to the control arm. Hypothesis tests are conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

Quality of Life Analyses

Quality of life analyses are performed using patients in the analysis populations for each quality of life instrument (EORTC-QLC-C30, EQ-5D-5L). EORTC-QLQ-30 and EQ-5D-5L results will be summarized at each visit by treatment group

For each EORTC QLQ-C30 administered, scores are computed for the following scales: Global Health Status, Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial difficulties.

Scoring is carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations are applied to the raw scores so that the reported score will have range 0-100 for all scales. Summary statistics are presented for each subscale. A summary health state index value is computed for each EQ-5D-5L assessment. Summary statistics are presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses are tabulated.

Safety Analysis

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events are reported by the MedDRA version 17.1 or higher. Toxicity is graded according to the NCI CTCAE version 4.03.

Safety analysis of patients in Part 1 is to include a summary of dose-limiting toxicity events.

The period for treatment-emergent adverse events and safety findings is from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event is then considered as treatment-emergent.

Tabular summaries are to be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events are to be summarized by System Organ Class and preferred term. All adverse event data is to be listed by patient.

Laboratory data is presented by cycle. Abnormal laboratory values are assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data are reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) are assessed. Shift to most severe toxicity grade are summarized.

Vital signs and ECG are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Vital signs are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Biomarker Subgroup Analysis

Analyses are performed to assess the associations between potential biomarkers (from plasma and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays are performed when appropriate.

Pharmacokinetics Analysis

Plasma concentrations of MM-398 and oxaliplatin can be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients can be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated (MM-398) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), are used to examine any possible interactions between MM-398 and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. NONMEM®, Version 7.3, is used to estimate individual PK parameters and simulate plasma exposures.

Example 4: Tolerability of Antineoplastic Therapies in Human Clinical Trial

The tolerability of antineoplastic therapies combining liposomal irinotecan, 5-FU/leucovorin and oxaliplatin was evaluated in a human clinical trial described in Example 3, using two different doses: 80 mg/m^2 (salt) of liposomal irinotecan (MM-398) and 60 mg/m^2 (salt) of liposomal irinotecan (MM-398). Table 15 summarizes three dosing regimens for the treatment of previously untreated (front-line) pancreatic cancer in humans over a 28 day treatment cycle.

Table 15 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
1	60	1, 15	2400/400	1, 15	80	1, 15
2	85	1, 15	2400/400	1, 15	80	1, 15
-2A[d]	75	1, 15	2400/400	1, 15	80	1, 15

a First dose administration in conjunction with first dose of nal-IRI; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle
Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

Initially, a combination of oxaliplatin, MM-398 liposomal irinotecan, leucovorin and 5-fluorouracil at dose level 1 in Table 15 above. The results are summarized in Table 16 for dose level 1 in Table 15 above (for 80 mg/m^2 (salt) M-398 dose), showing that the 80 mg/m^2 (salt) dose of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin at dose level 1 was not tolerated in humans.

Table 16: Antineoplastic Therapy with 80 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 3 Day 15
1	✓	✓	X	X	X	X
2	✓	R	R	R	X	X
3	✓	X	X	X	X	X

4	✓	✓	X	X	X	X
5	✓	X	X	X	X	X
6	✓	✓	R	R	R	R
7	✓	X	X	X	X	X

Table 16 summarizes the results from treating a total of seven (7) patients as part of Part 1 of Arm 1 shown in Figure 12. All seven patients met the applicable inclusion criteria specified below, including a diagnosis of pancreatic cancer.

A "check mark" (✓) in Table 16 indicates the patient received the antineoplastic therapy of dose level 1 in Table 15 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R" in Table 16 indicates the patient received a reduced dose of antineoplastic therapy of dose level -1 in Table 2 (Example 3 above) on the corresponding cycle and day: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

An "X" in Table 16 indicates the patient did not receive an antineoplastic therapy combining liposomal irinotecan, oxaliplatin, 5-fluorouracil and leucovorin or combining liposomal irinotecan, oxaliplatin, and 5-fluorouracil. After cycle 1, day 1 and prior to cycle 1, day 15, patient 2 was determined to be homozygous for the UGT1A1*28 allele, and subsequent reduced doses of the antineoplastic therapy were administered on days indicated in Table 16, based on the protocol of Example 3. Patients 1 and 3-7 were not homozygous for UGT1A1*28 allele.

The antineoplastic therapy of dose level 1 in Table 15 (Example 4) was only administered to 2 of these 6 patients on day 15 of (28-day) cycle 1, no patients received dose level 1 for more than 2 consecutive doses, and none of the patients received this therapy after cycle 1.

Accordingly, as noted in the Table 16, antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of

5-fluorouracil and (l+d) leucovorin were not well tolerated in a human clinical trial (resulting in dose limiting toxicities). Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 15.

In contrast, as noted in Table 18 below, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m2 of 5-fluorouracil and (l+d) leucovorin were tolerated in a human clinical trial. In particular, dose level -1 in Table 17 (a 60 mg/m^2 (salt) M-398 dose) was administered two or more consecutive times to multiple human patients in the clinical trial described in Example 3. These antineoplastic therapies comprising the reduced 60 mg/m^2 (salt) of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin were better tolerated in humans than dose level 1 in Table 15. In other embodiments, patients are administered the therapy of dose level -2B in Table 17.

Table 17 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Table 18: Antineoplastic Therapy with 60 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1
1	✓	✓	R2	R2	R2
2	✓	✓	✓		
3	✓	✓	✓		
4	✓	✓			

5	✓	✓	✓		

Table 18 summarizes the results from treating a total of five (5) patients as part of Part 1 of Arm 1 shown in Figure 12. All five patients met the applicable inclusion criteria specified in Example 3, including a diagnosis of pancreatic cancer. A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

In contrast to the antineoplastic therapy of dose level 1 in Table 14, the antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered repeatedly to patients 2 and 6 for at least 3 consecutive administrations (including 4 consecutive administrations for patient 6).

The antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered to 5 of 5 patients on days 1 and 15 of (28-day) cycle 1, and days 1 and 15 of (28 day) to 3 of 4 patients in the study, with no dose limiting toxicities. The antineoplastic therapy of dose level -1 was administered repeatedly to all 5 patients for at least 2 consecutive administrations.

A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R2" in Table 18 indicates the patient received a reduced dose of antineoplastic therapy of dose on the corresponding cycle and day: 50 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 1,800 mg/m^2 5-fluorouracil (a 25% reduction compared to dose level -1 dose), as described in the protocol of Example 3. One patient in

Table 18 received this reduced dose in response to Grade II symptoms (non-hematologic), but without a dose limiting toxicity.

Accordingly, as noted in the Table 18, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin were well tolerated in a human clinical trial. Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 17.

Example 5: ONIVYDE® (irinotecan liposome injection) Liposomal Irinotecan

One preferred example of an irinotecan liposome described herein is the product marketed as ONIVYDE® (irinotecan liposome injection). ONIVYDE® is a topoisomerase inhibitor, formulated with irinotecan in a liposomal dispersion, for intravenous use.

The finished ONIVYDE® product is a white to slightly yellow opaque sterile concentrate for infusion. It consists of an isotonic dispersion of liposomes containing irinotecan hydrochloride trihydrate. The liposomes are small unilamellar lipid bilayer vesicles, approximately 110 nm in diameter, enclosing an aqueous compartment that contains irinotecan in a gelated or precipitated state, as sucrosofate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL. The liposomes are dispersed in an aqueous buffered solution.

The ONIVYDE® product contains irinotecan sucrosofate encapsulated in a liposome, obtained from an irinotecan hydrochloride trihydrate starting material. The chemical name of irinotecan is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. The dosage of ONIVYDE® can be calculated based on the equivalent amount of irinotecan trihydrate hydrochloride starting material used to prepare the irinotecan liposomes, or based on the amount of irinotecan in the liposome. There are about 866 mg of irinotecan per gram of

irinotecan trihydrate hydrochloride. For example, an ONIVYDE® dose of 80 mg based on the amount of irinotecan hydrochloride trihydrate starting material actually contains about 0.866x(80mg) of irinotecan in the final product (i.e., a dose of 80 mg/m^2 of ONIVYDE® based on the weight of irinotecan hydrochloride starting material is clinically equivalent to about 70 mg/m^2 of irinotecan in the final product). Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL.

Claims

1. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.
2. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 85 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.
3. The use of any one of claims 1-2, wherein the 5-fluorouracil is administered as an infusion over 46 hours.
4. The use of any one of claims 1-3, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.
5. The use of any one of claims 1-4, wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle.
6. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not

previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 60 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle.

7. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 85 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

8. The use of any one of claims 1-7, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.
9. The use of any one of claims 1-8, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.
10. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 60 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

11. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
a. 60 mg/m^2 of liposomal irinotecan,
b. 85 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

12. The use of any one of claims 1-9, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

13. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
a. 60 mg/m^2 of liposomal irinotecan,
b. 60 mg/m^2-85mg/m^2 oxaliplatin,

c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

14. The use of any one of claims 1-11, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

15. The use of any one of claims 1-8, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

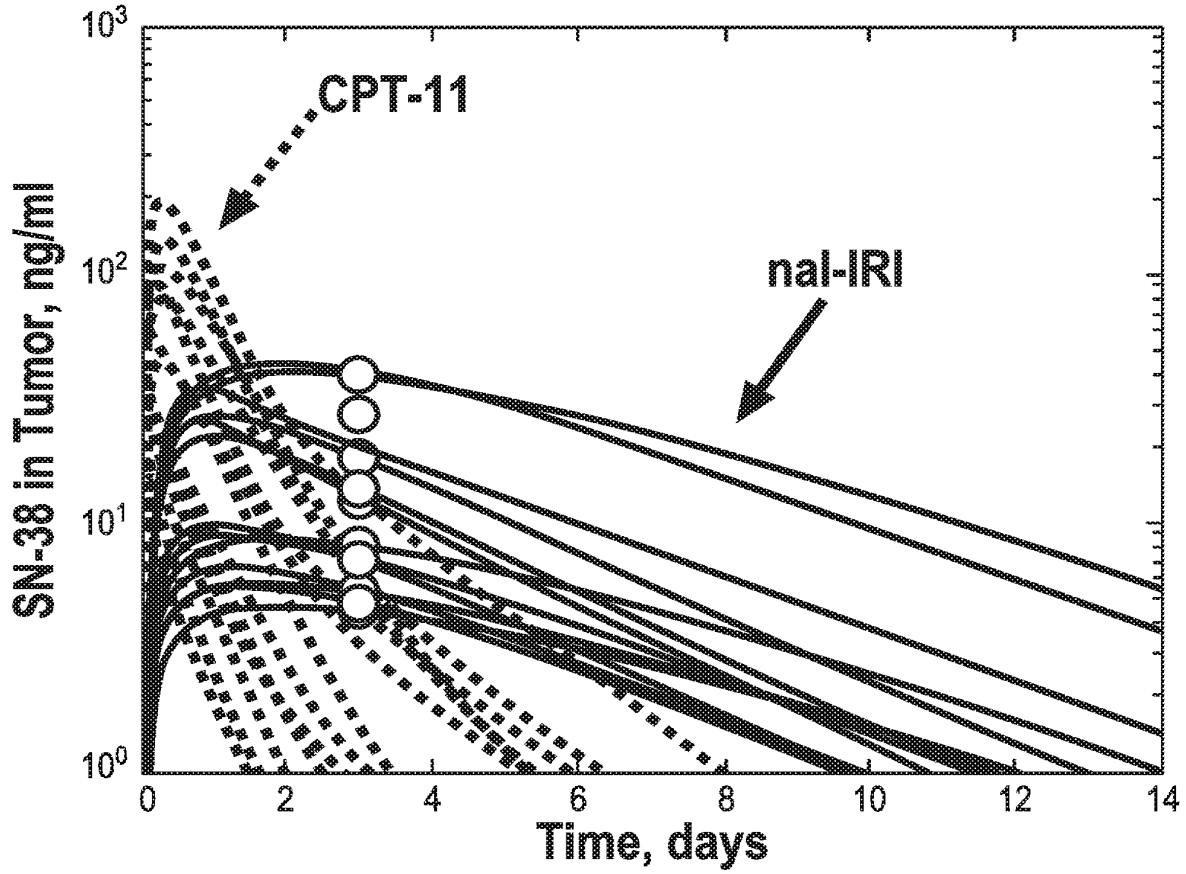

CPT-11
nal-IRI
SN-38 in Tumor, ng/ml
10^3
10^2
10^1
10^0
0
2
4
6
8
10
12
14
Time, days

FIG. 1A

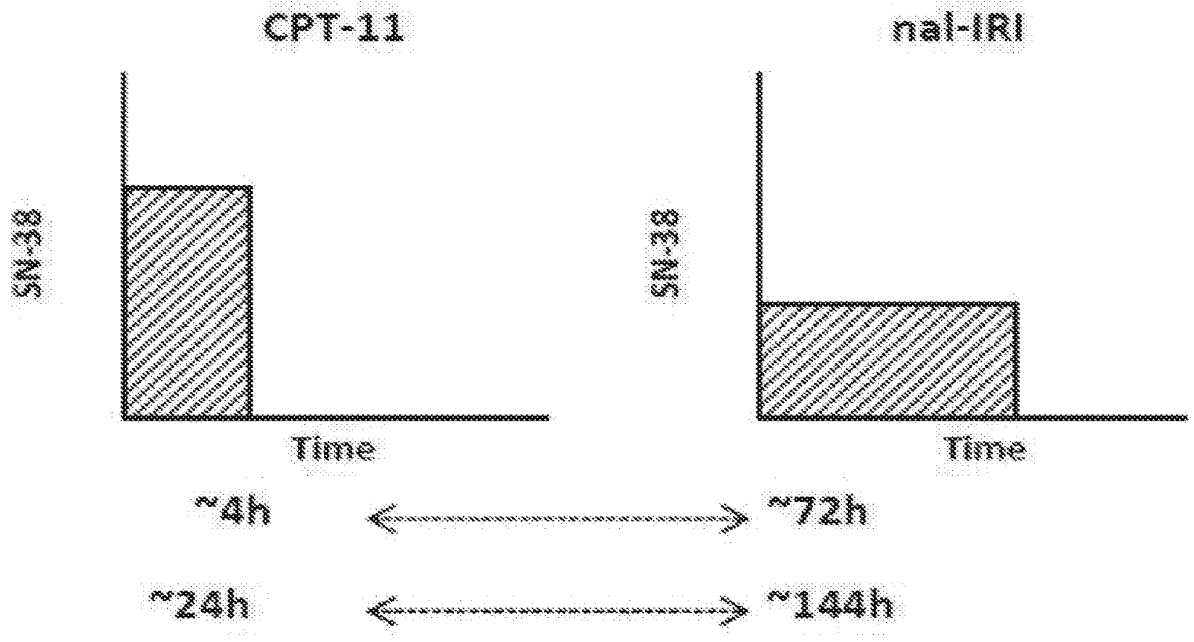

CPT-11
nal-IRI
SN-38
SN-38
Time
Time
~4h
~72h
~24h
~144h

FIG. 1B

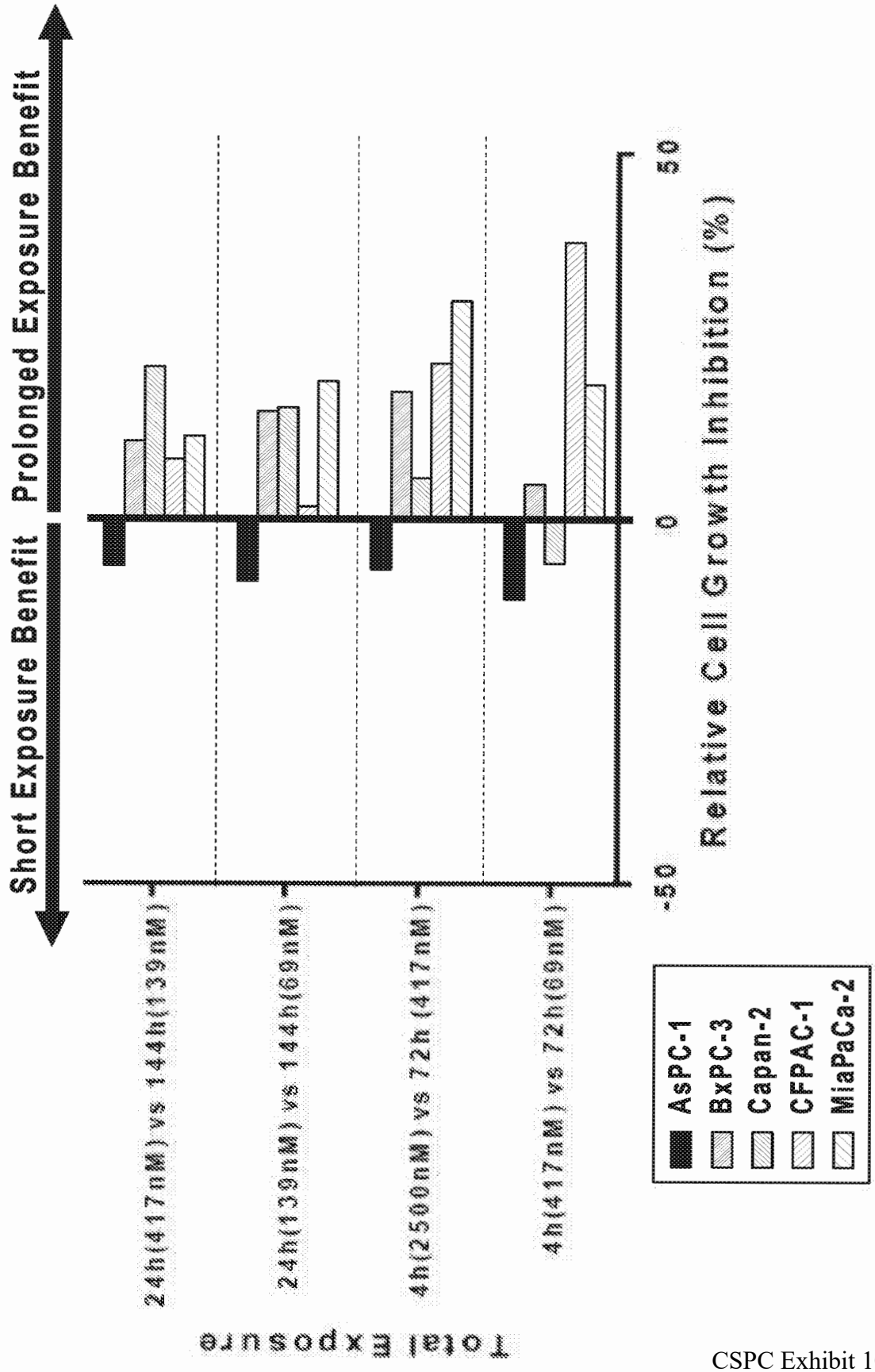

Short Exposure Benefit
Prolonged Exposure Benefit
Total exposure
24h(417nM) vs 144h(139nM)
24h(139nM) vs 144h(69nM)
4h(2500nM) vs 72h (417nM)
4h(417nM) vs 72h(69nM)
-50
0
50
Relative Cell Growth Inhibition (%)
AsPC-1
BxPC-3
Capan-2
CFPAC-1
MiaPaCa-2

FIG. 1C

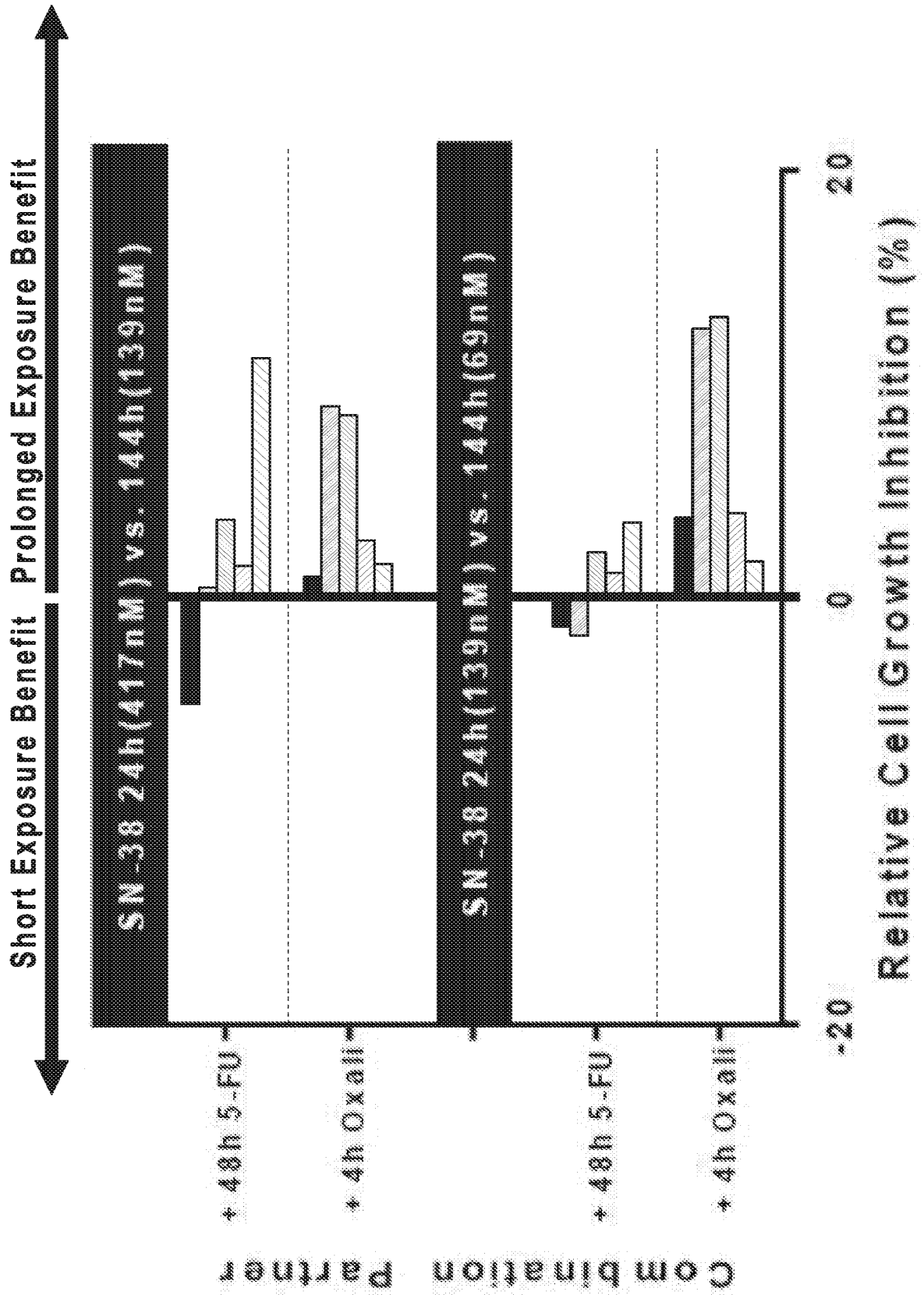

Short Exposure Benefit
Prolonged Exposure Benefit
SN-38 24h(417nM) vs. 144h(139nM)
SN-38 24h(139nM) vs. 144h(69nM)
+ 48h 5-FU
+ 4h Oxali
+ 48h 5-FU
+ 4h Oxali
Combination Partner
-20
0
20
Relative Cell Growth Inhibition (%)

FIG. 1D

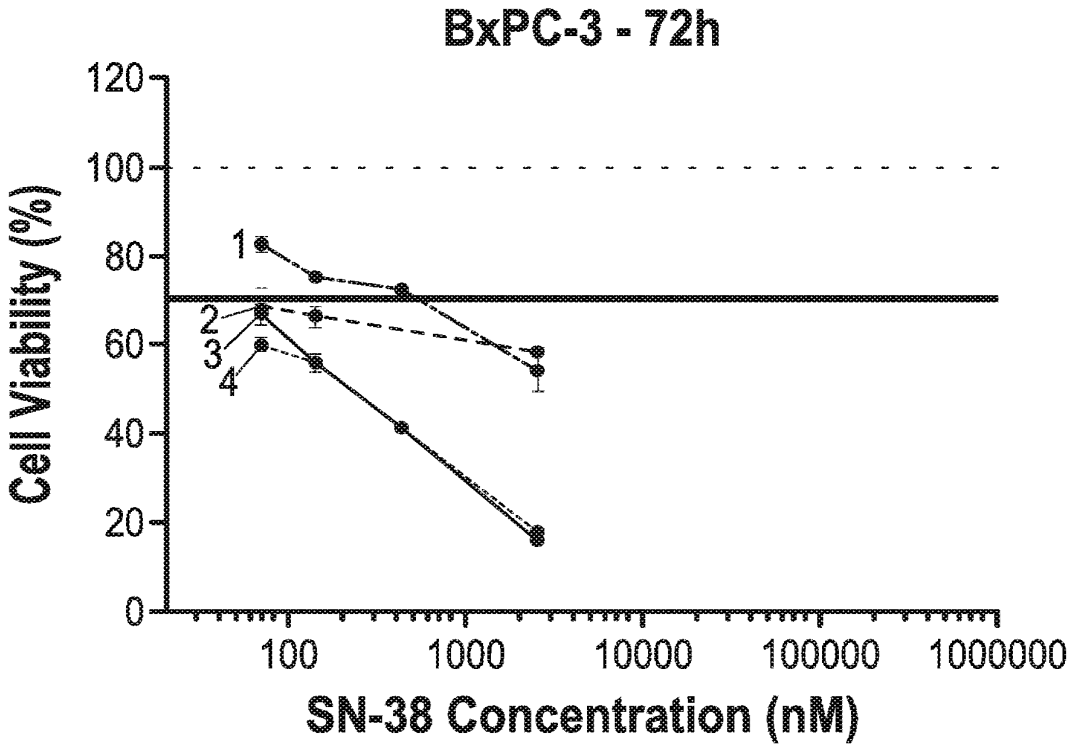

BxPC-3 - 72h
Cell Viability (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 Concentration (nM)

FIG. 2A

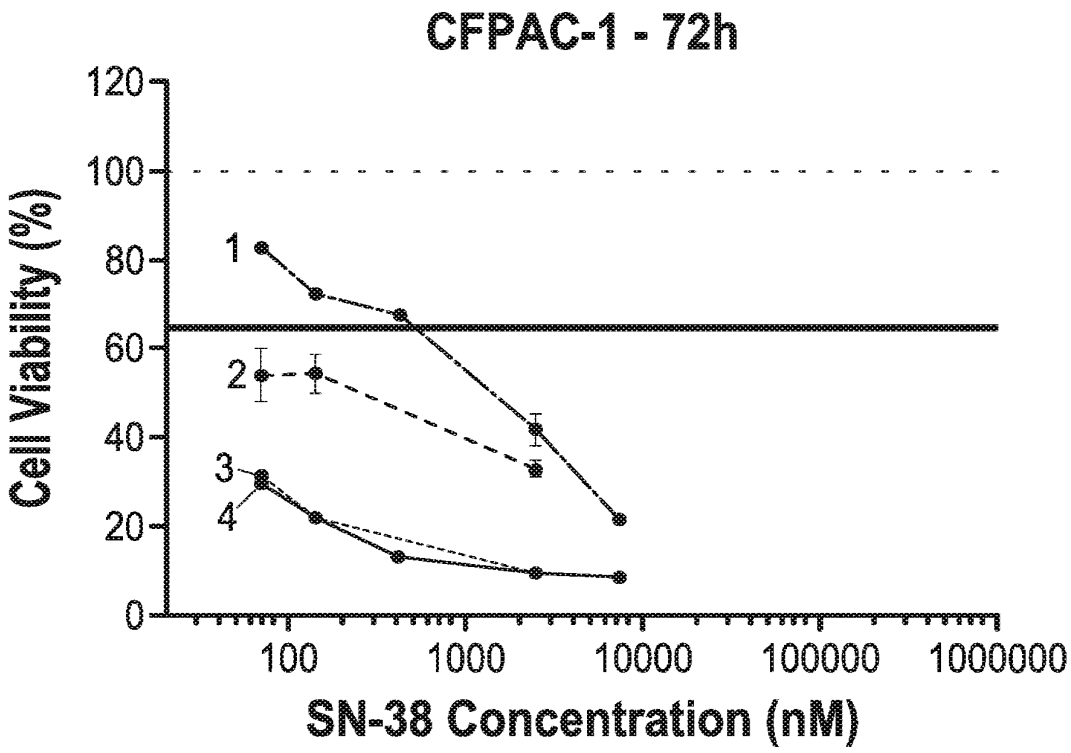

CFPAC-1 - 72h
Cell Viability (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 Concentration (nM)

FIG. 2B

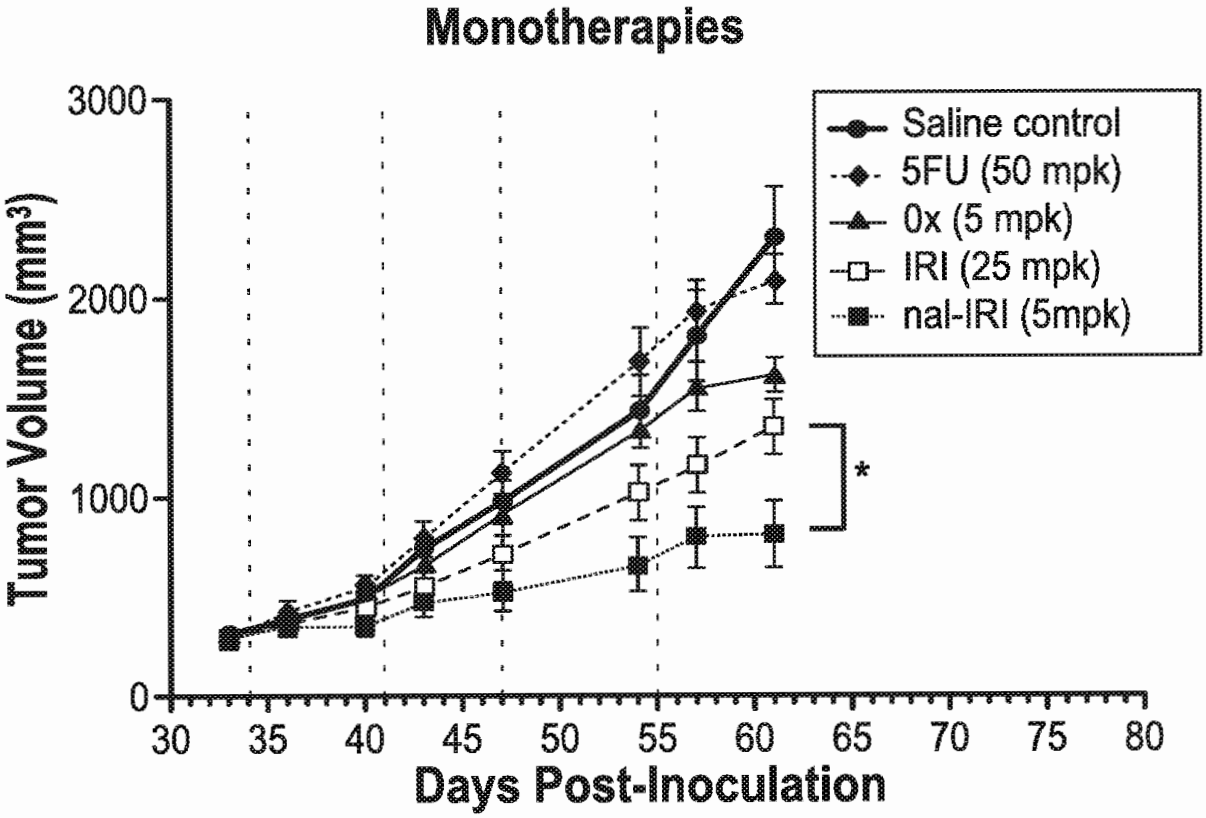

Monotherapies
Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
5FU (50 mpk)
0x (5 mpk)
IRI (25 mpk)
nal-IRI (5mpk)
*

FIG. 3A

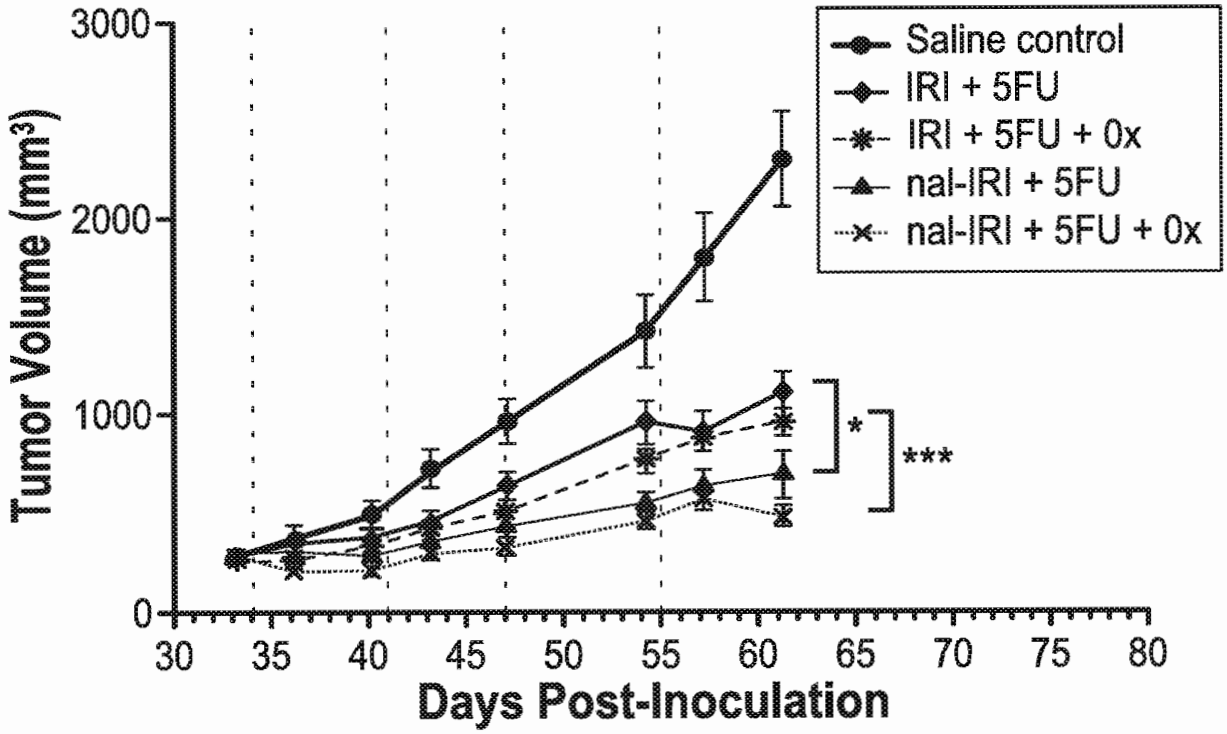

Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
IRI + 5FU
IRI + 5FU + 0x
nal-IRI + 5FU
nal-IRI + 5FU + 0x
*
***

FIG. 3B

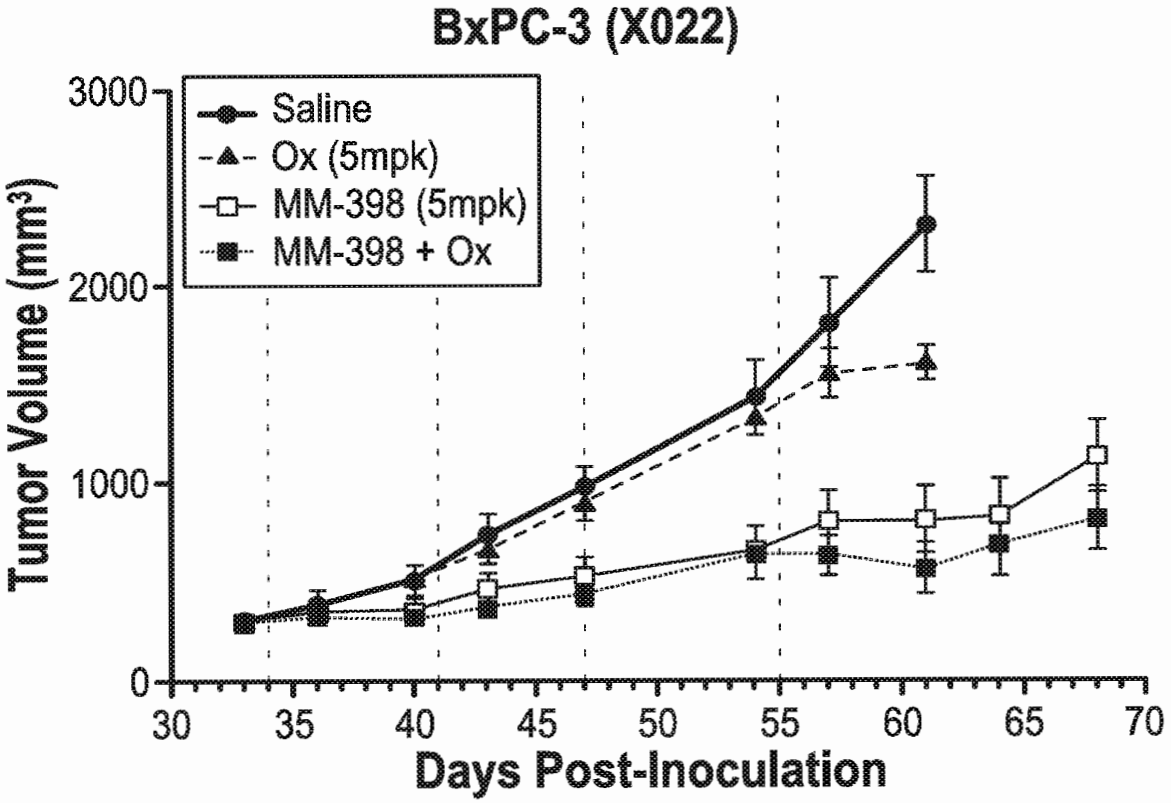

BxPC-3 (X022)
Saline
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
Days Post-Inoculation

FIG. 4A

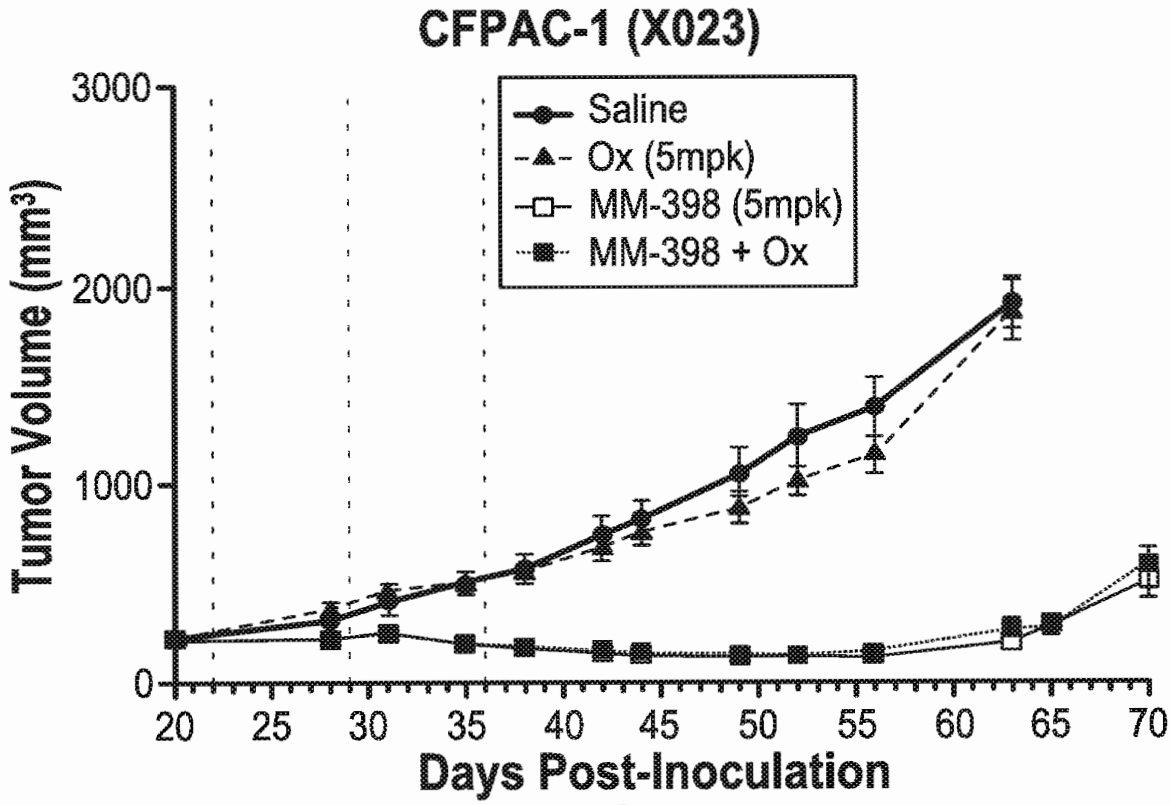

CFPAC-1 (X023)
Saline
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
Tumor Volume (mm³)
3000
2000
1000
0
20
25
30
35
40
45
50
55
60
65
70
Days Post-Inoculation

FIG. 4B

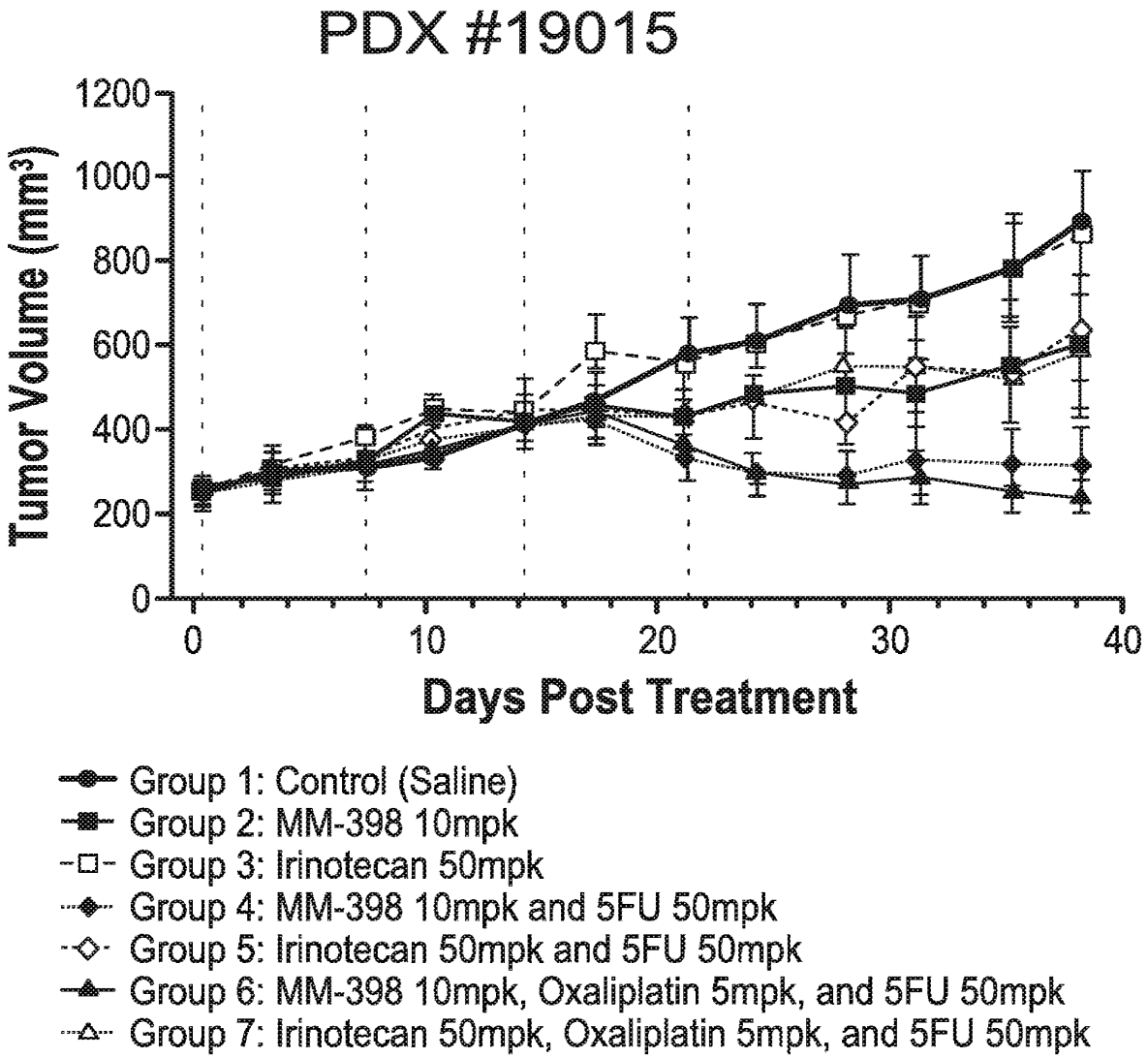

PDX #19015
Tumor Volume (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
Days Post Treatment
Group 1: Control (Saline)
Group 2: MM-398 10mpk
Group 3: Irinotecan 50mpk
Group 4: MM-398 10mpk and 5FU 50mpk
Group 5: Irinotecan 50mpk and 5FU 50mpk
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk
Group 7: Irinotecan 50mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5A

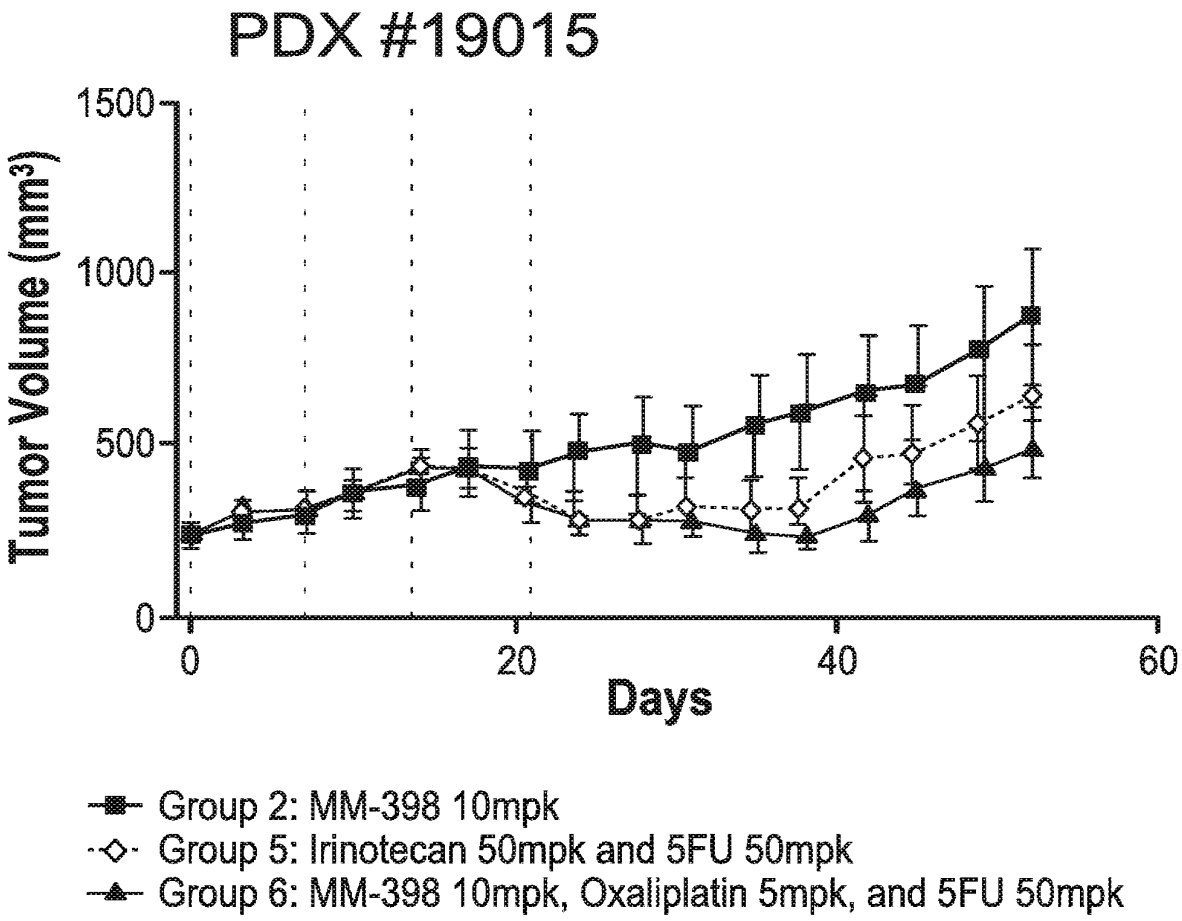

PDX #19015
Tumor Volume (mm³)
1500
1000
500
0
0
20
40
60
Days
Group 2: MM-398 10mpk
Group 5: Irinotecan 50mpk and 5FU 50mpk
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5B

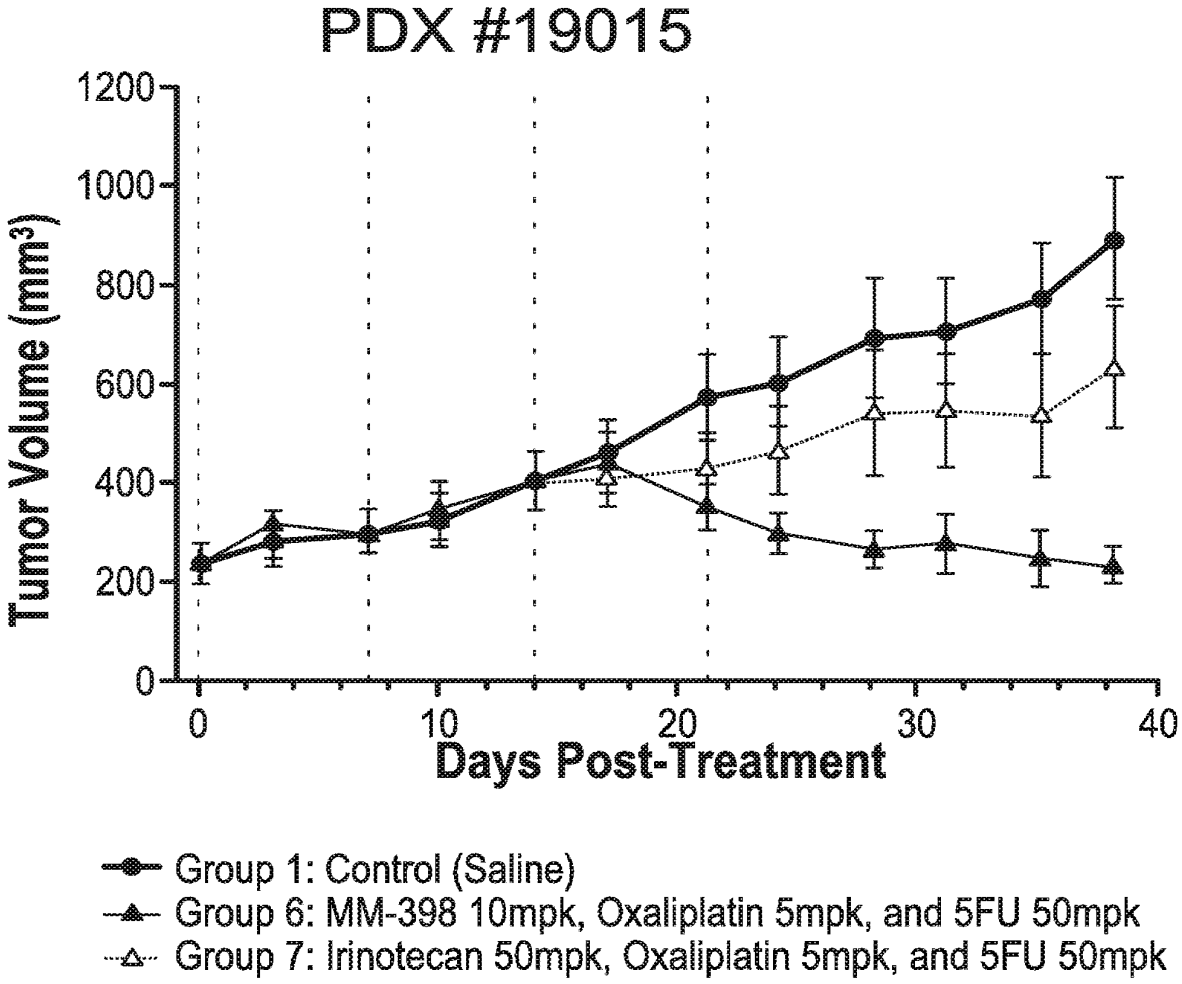

PDX #19015
Tumor Volume (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
Days Post-Treatment
Group 1: Control (Saline)
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk
Group 7: Irinotecan 50mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5C

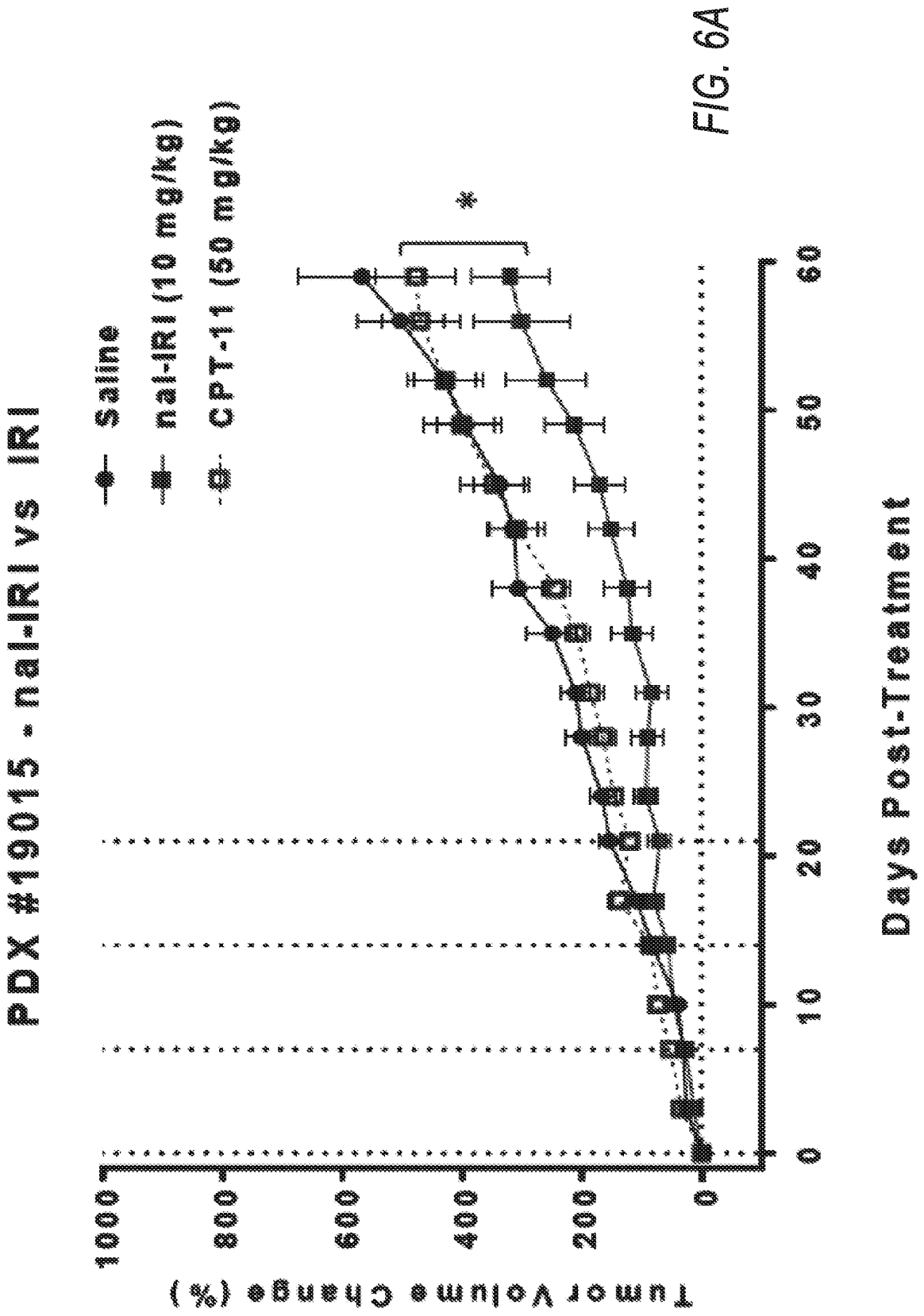

PDX #19015 - nal-IRI vs IRI
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6A

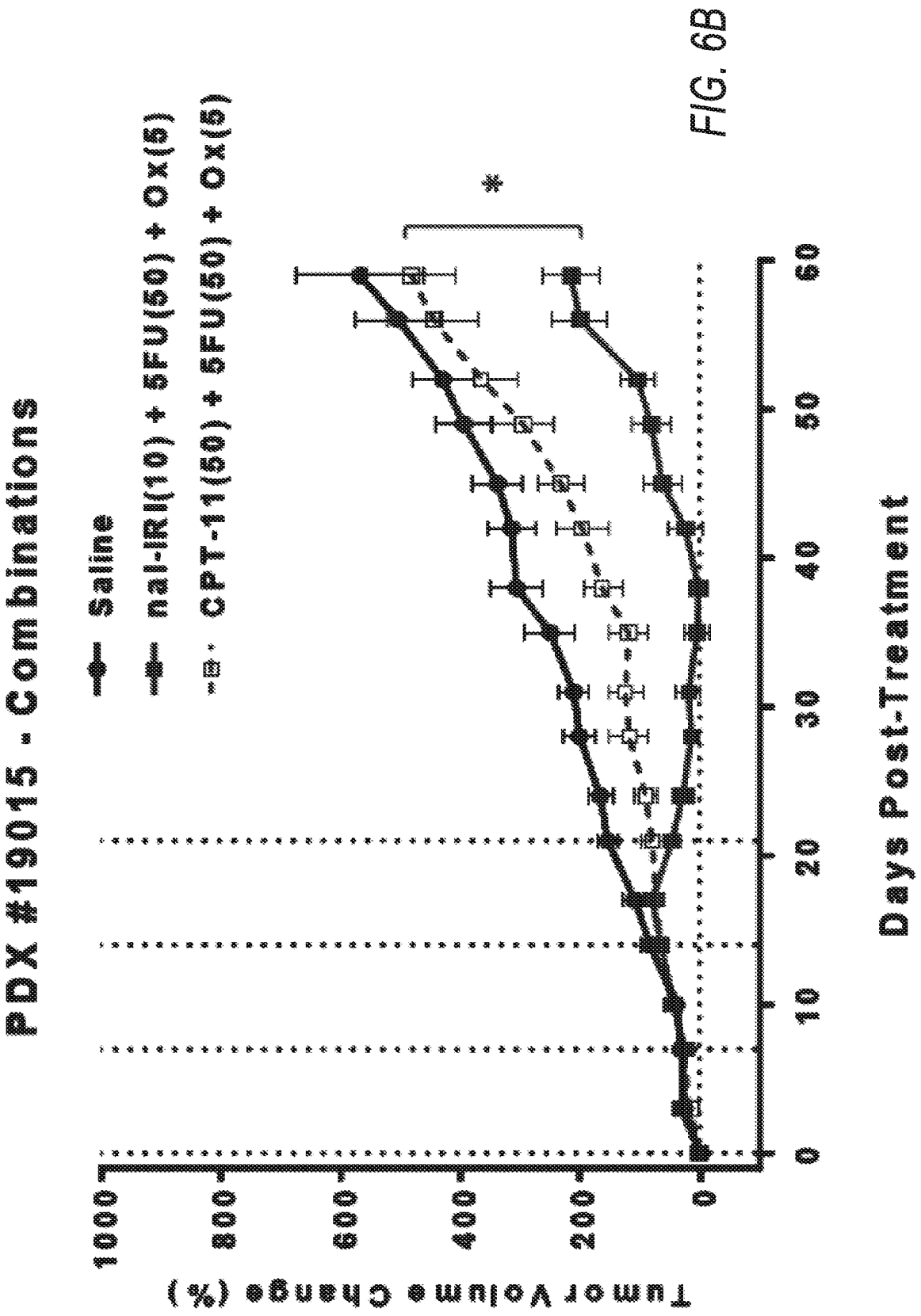

PDX #19015 - Combinations
Saline
nal-IRI(10) + 5FU(50) + Ox(5)
CPT-11(50) + 5FU(50) + Ox(5)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6B

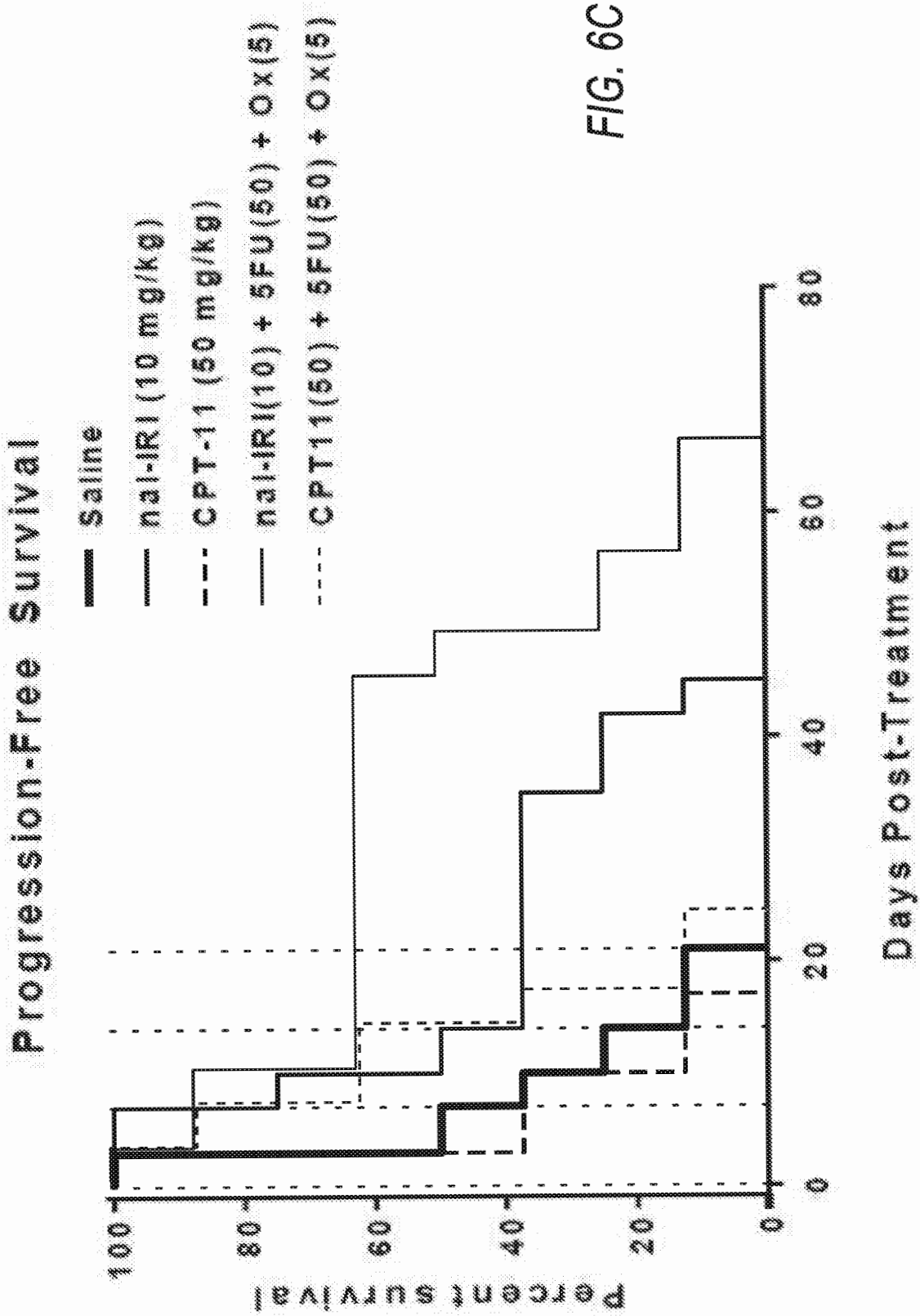
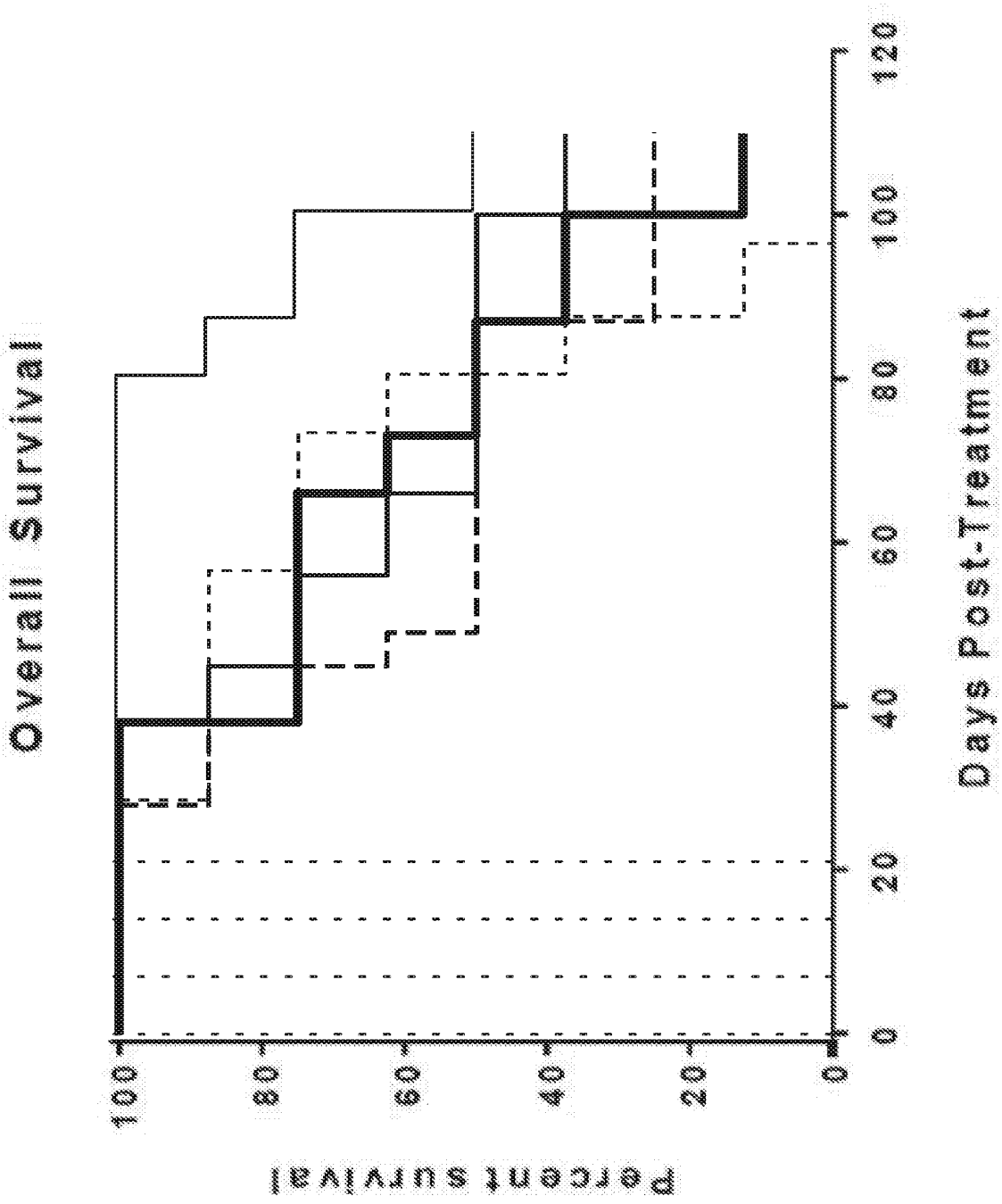

Progression-Free Survival
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(50) + Ox(5)
Percent survival
100
80
60
40
20
0
0
20
40
60
80
Days Post-Treatment

FIG. 6C

FIG. 6D


Overall Survival
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
120
Days Post-Treatment

G1 – Control
G2 – MM-398 10 mpk
G3 – Irinotecan 50 mg/kg
G4 – MM-398 10 mpk + 5FU 50 mpk
G5 – Irinotecan 50 mpk + 5FU 50 mpk
G6 – MM-398 10 mpk + 5FU 50 mpk + Ox 5 mpk
G7 – Irinotecan 50 mpk + 5FU 50 mpk + Ox 5 mpk

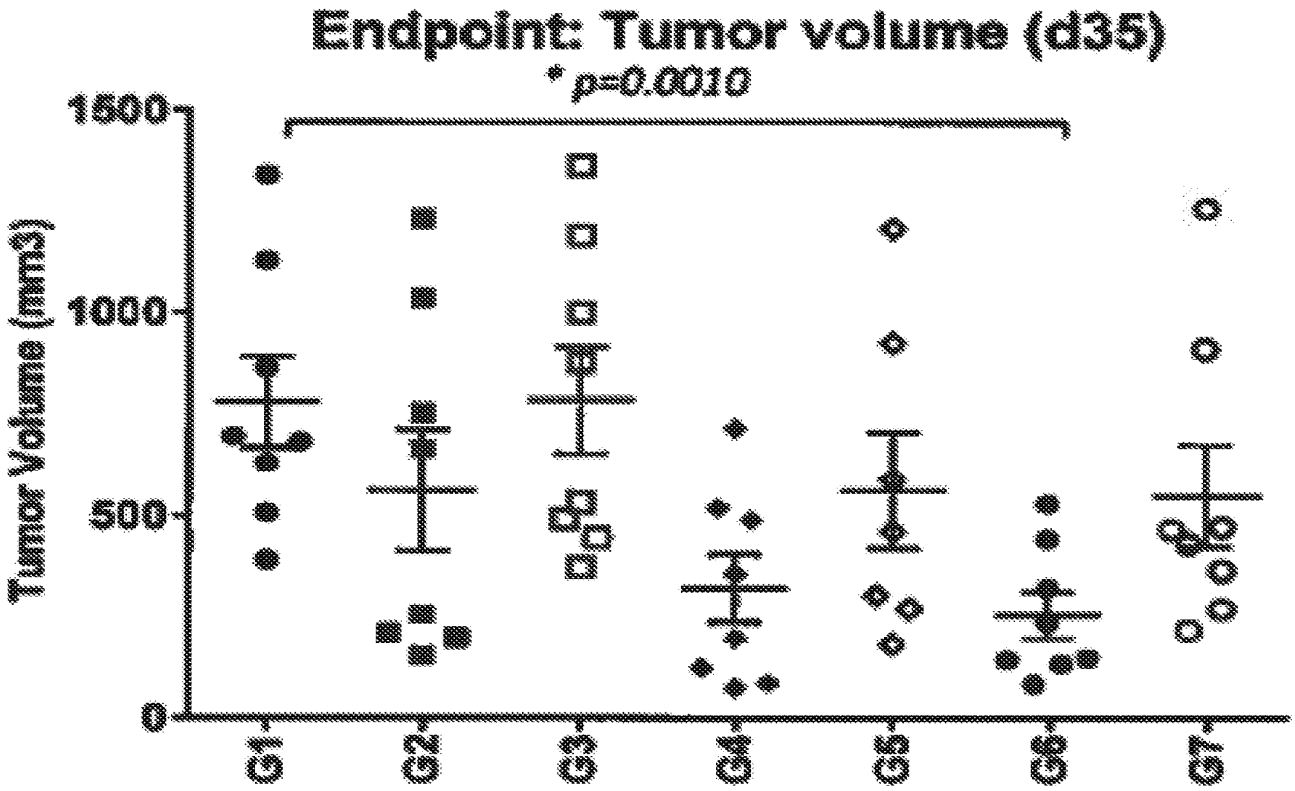


FIG. 7

	Control	MM-398	IRI	NAPOLI	FOLFIRI	NAPOX	FOLFIRINOX
Tumor Vol (mean mm^3,d35)	779	562	753	321	523	255	445
TGI (% at d35)	n/a	27.9%	3.4%	58.8%	32.9%	67.3%	42.9%
Median Days to 1000mm^3	50.5 (n=8 of 8)	68 (6 of 8, 2 est)	43.5 (8 of 8)	70 (6 of 8, 2 est)	56 (7 of 7)	77 (8 of 8)	56 (8 of 8)
Stable Disease (-30% - +30%)	0	3	1	2	3	2	4
PR (30%-95% reduction)	0	0	0	3	0	4	0
CR (≥95% reduction)	0	0	0	0	0	0	0
Response Rate (≥30% reduction)	0%	0%	0%	38%	0%	50%	0%
Disease Control	0%	38%	13%	63%	38%	75%	50%
Rate (ORR + SD)							
Median Progression Free Survival (days)	5	12	3	36.5	10	47	14
Median OS(days)	80	83	68	100	80	105	80

FIG. 8

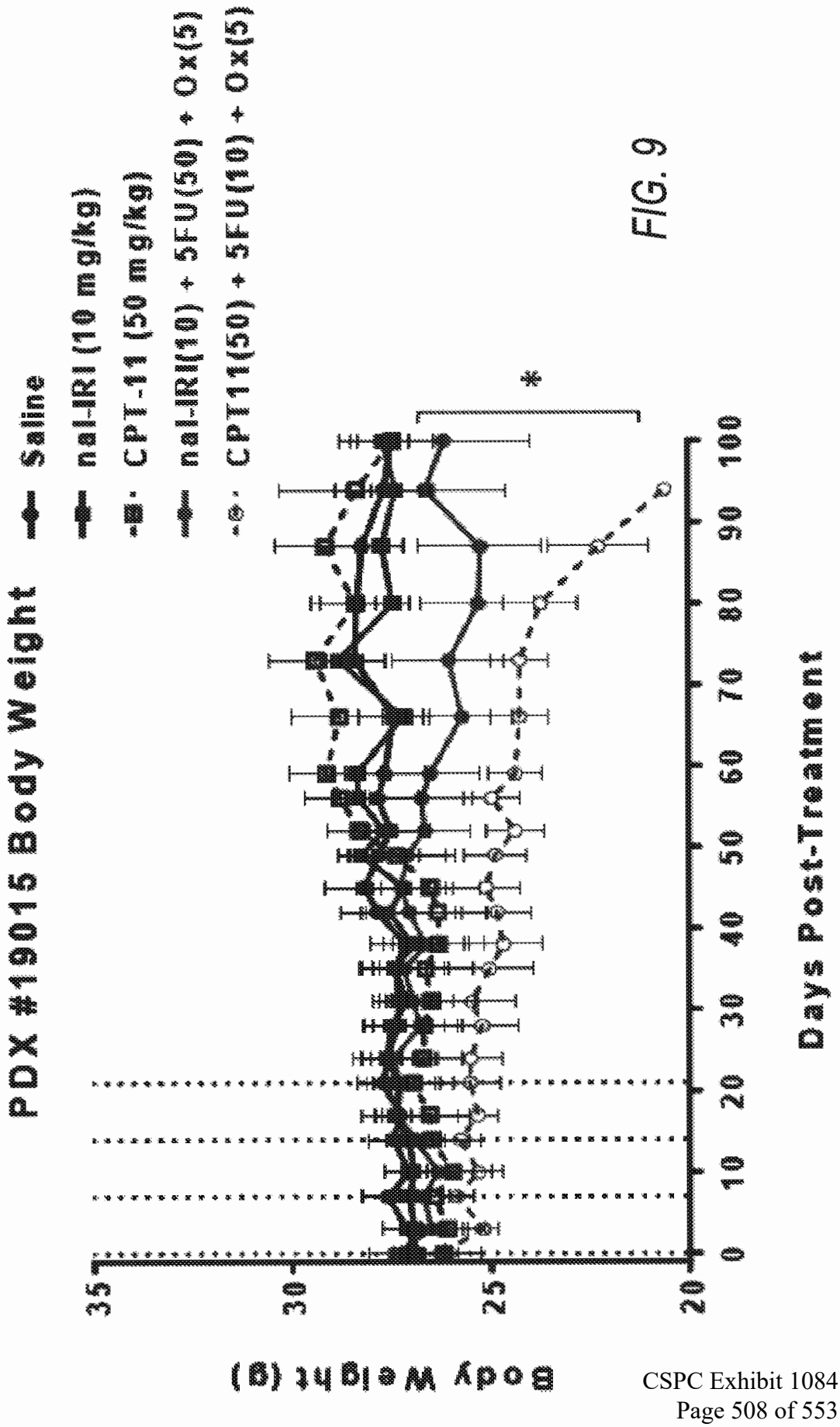

PDX #19015 Body Weight
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(10) + Ox(5)
*
Body Weight (g)
35
30
25
20
0
10
20
30
40
50
60
70
80
90
100
Days Post-Treatment

FIG. 9

FIG. 10A

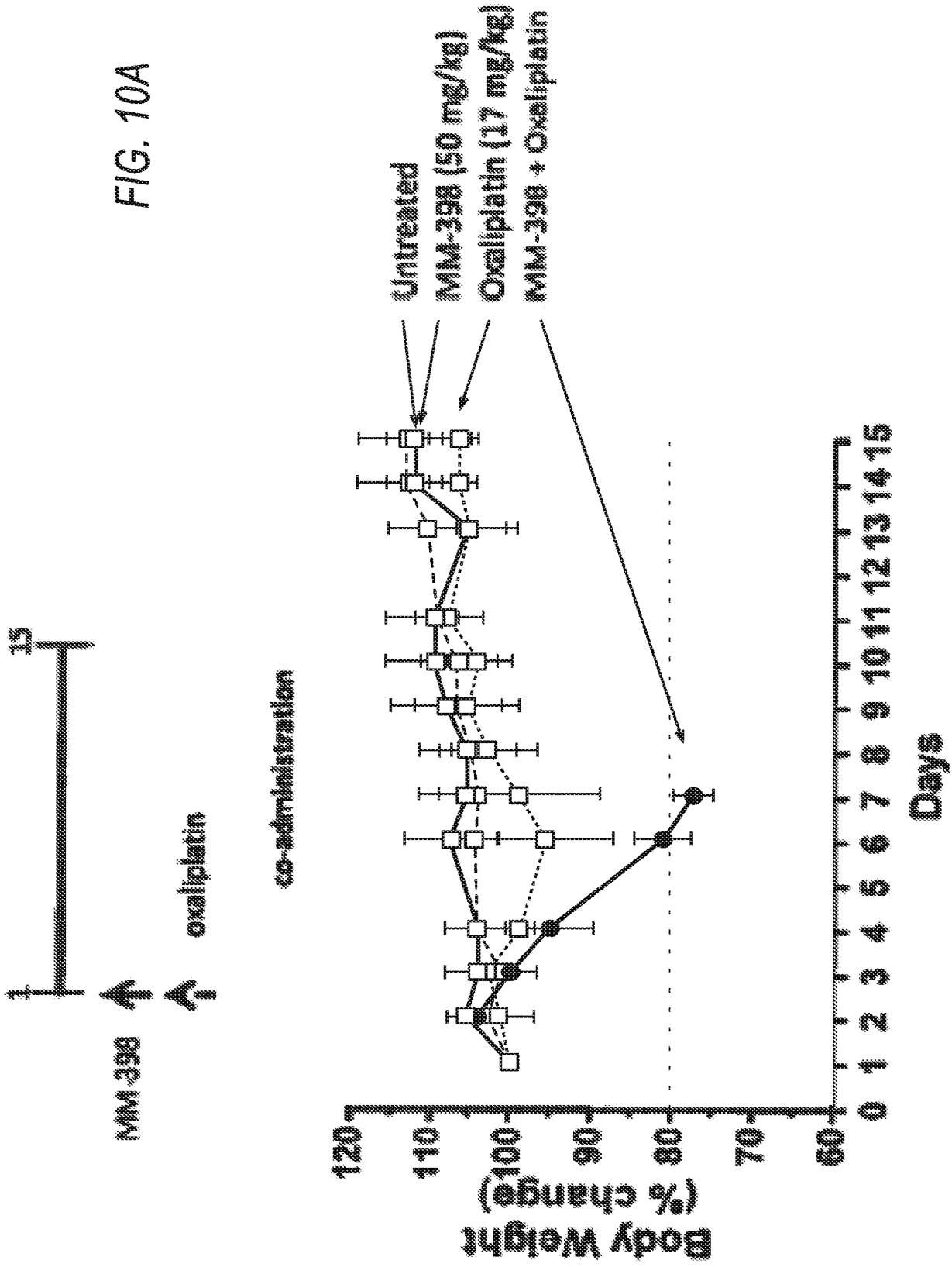
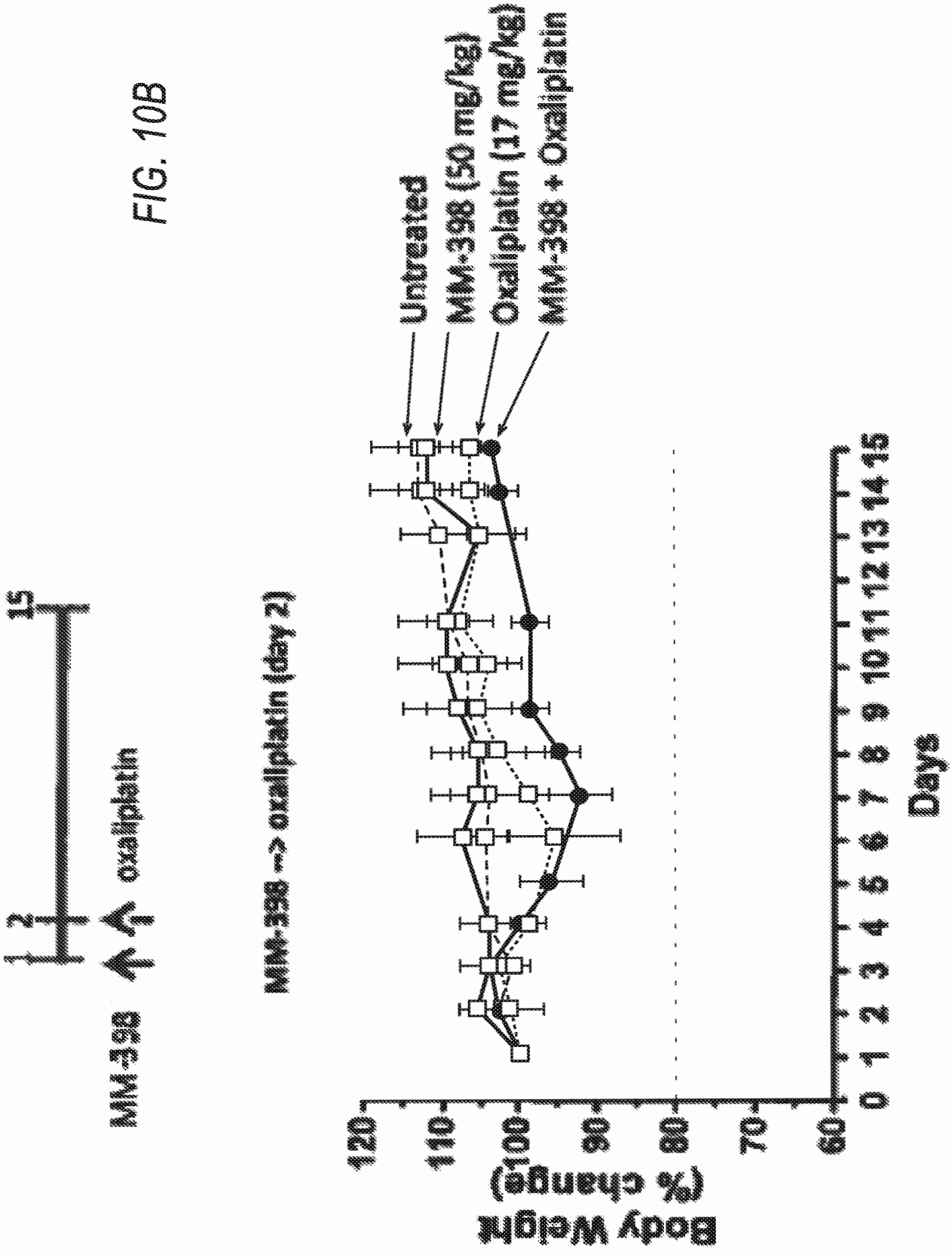

Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin
Body Weight (% change)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days
co-administration
MM-398
oxaliplatin
1
13

FIG. 10B


MM-398
oxaliplatin
1
2
15
MM-398 --> oxaliplatin (day 2)
Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin
Body Weight (% change)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days

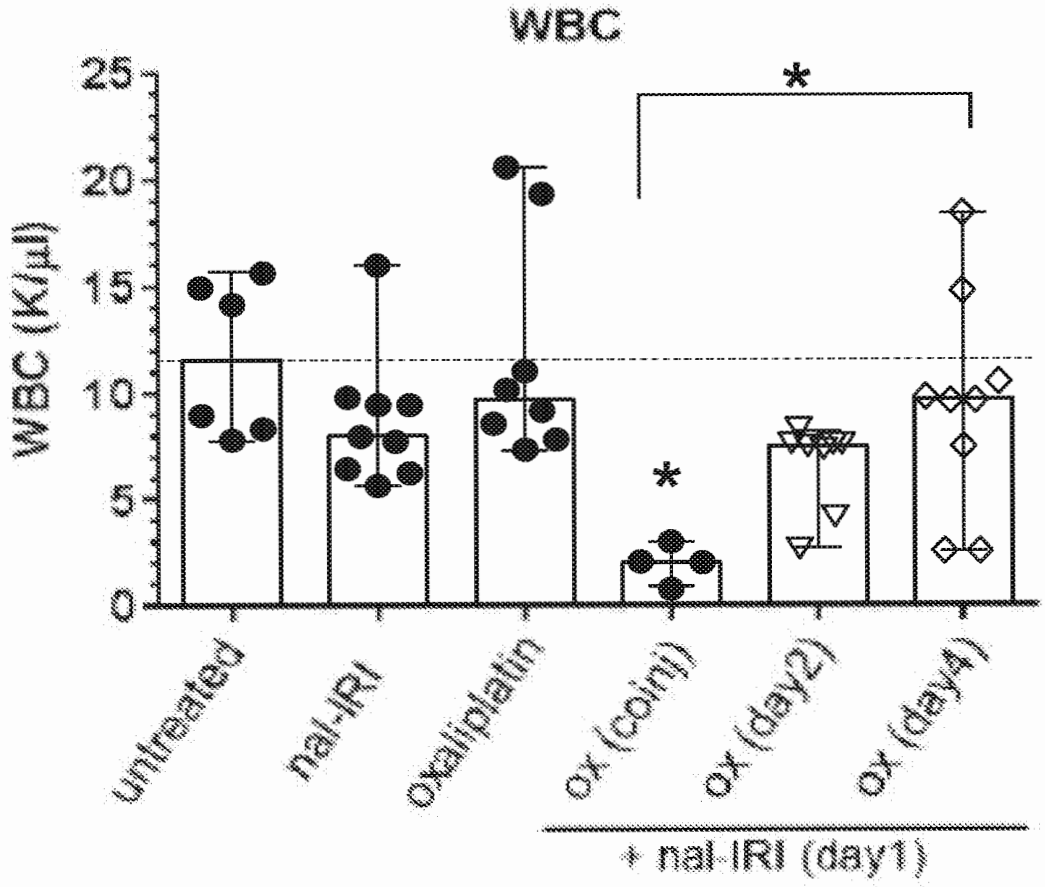


FIG. 11A

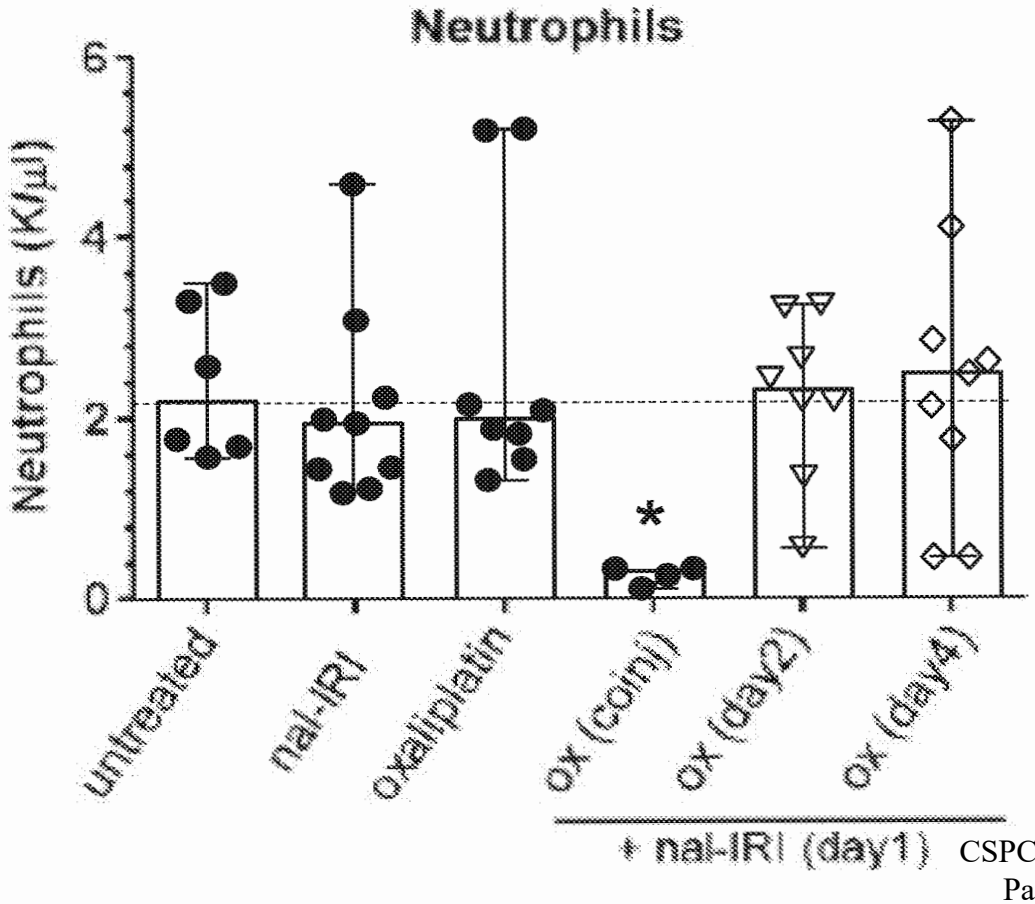


FIG. 11B

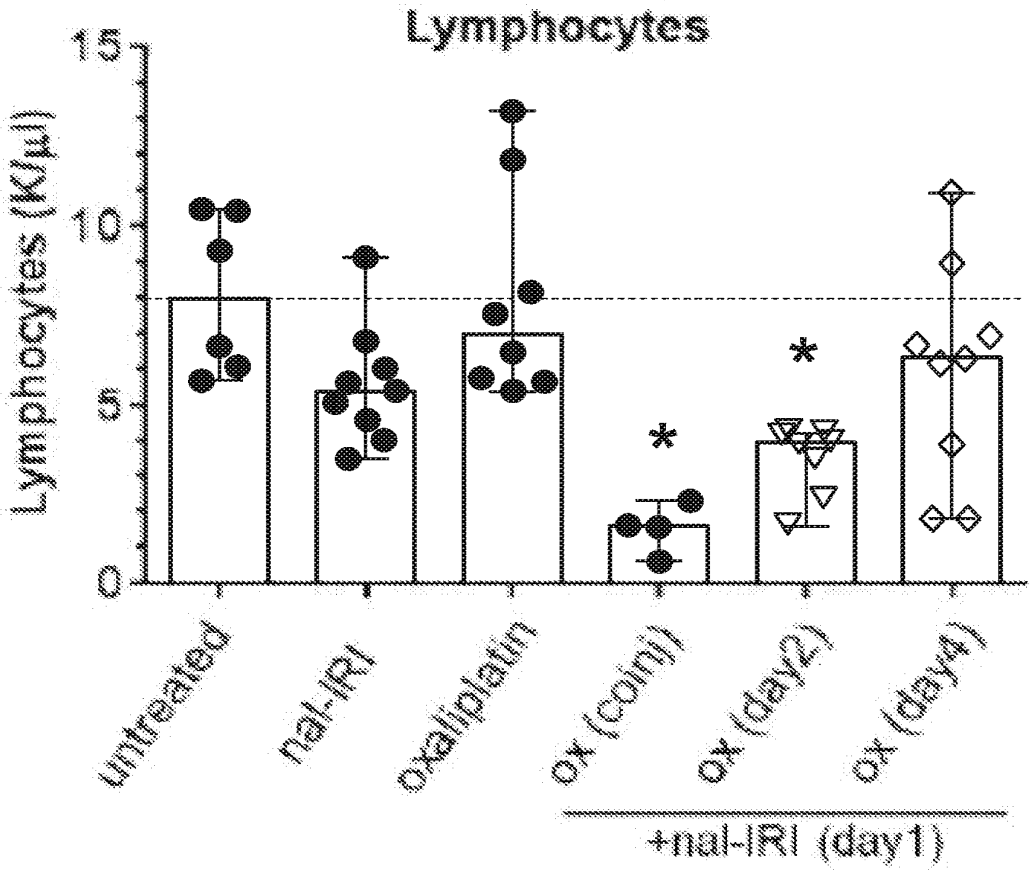


FIG. 11C

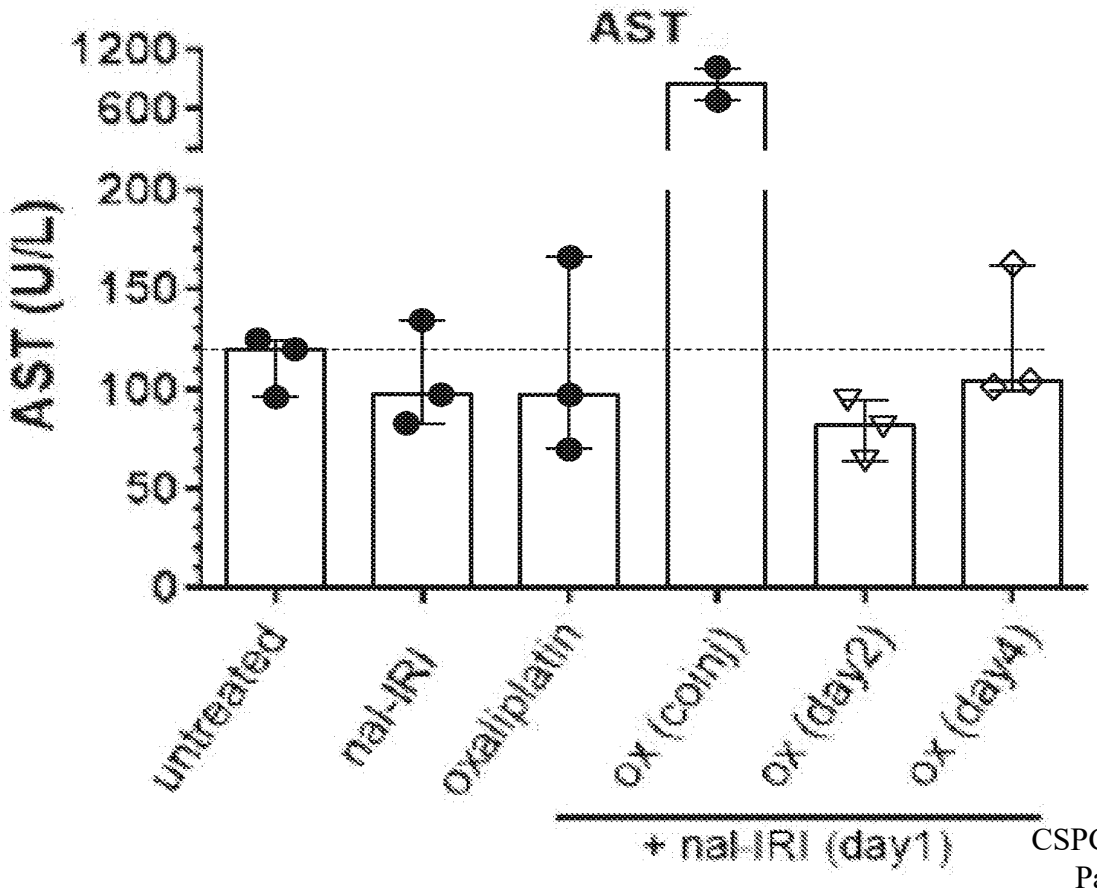


FIG. 11D

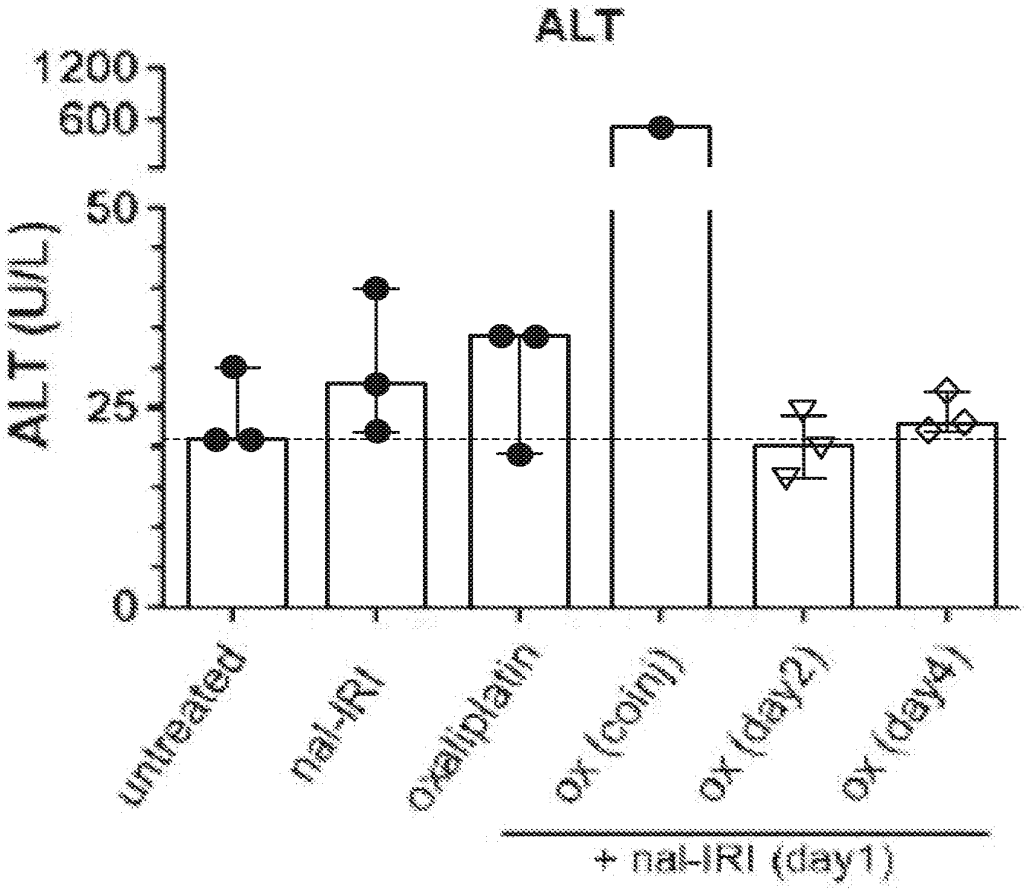


FIG. 11E

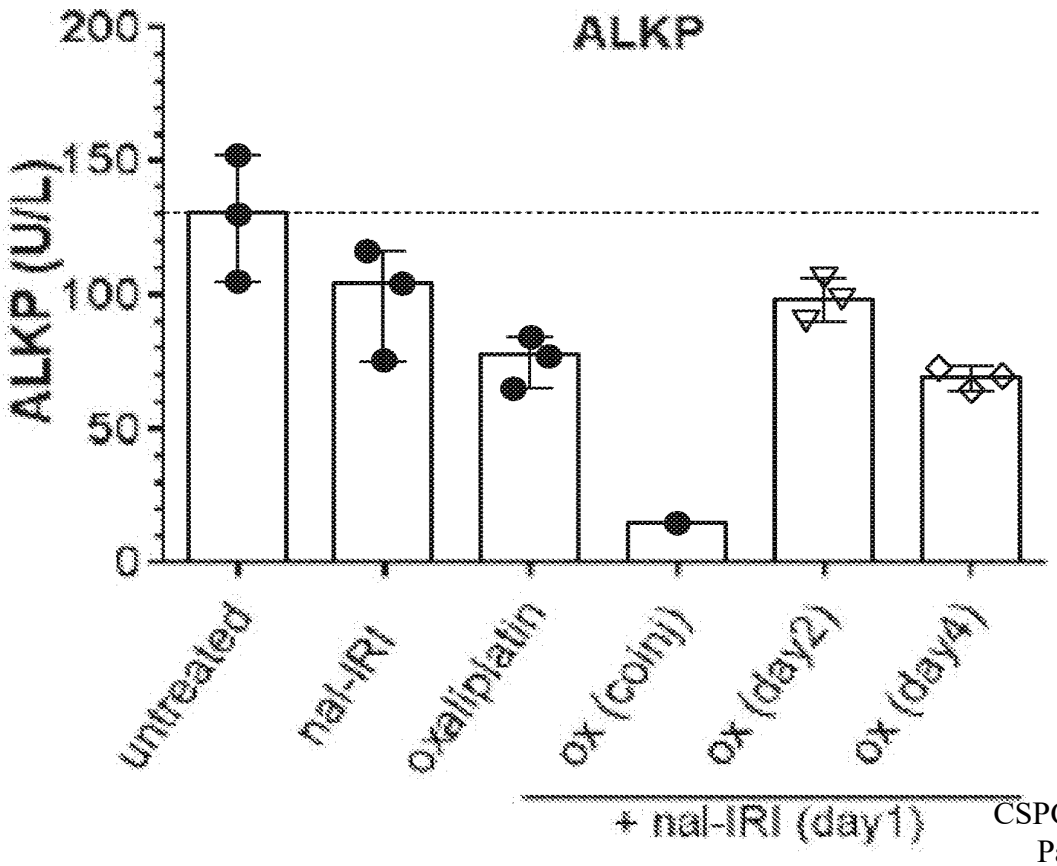


FIG. 11F

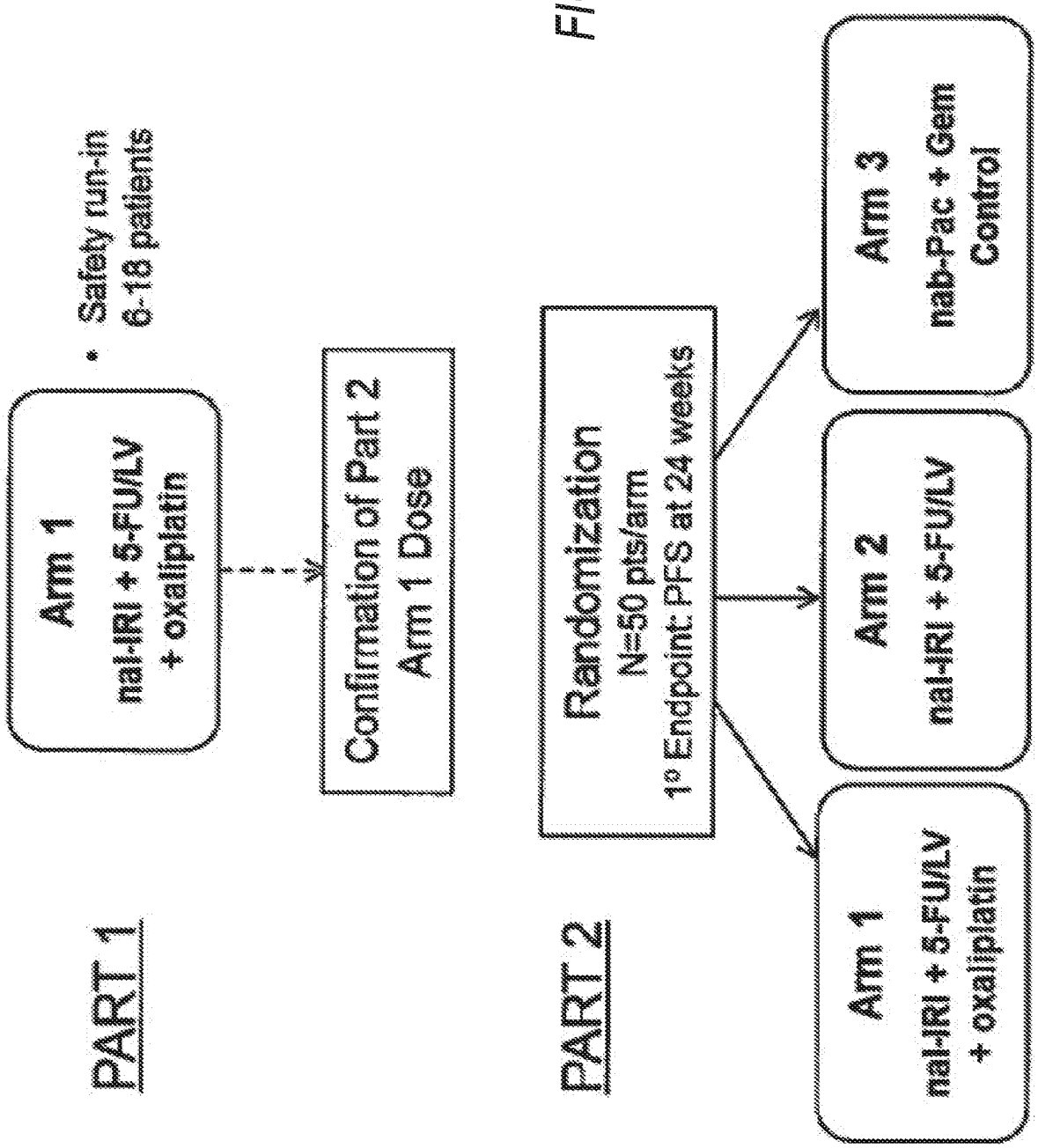

PART 1
Arm 1
mal-IRI + 5-FU/LV
+ oxaliplatin
* Safety run-in
6-18 patients
Confirmation of Part 2
Arm 1 Dose
PART 2
Randomization
N=50 pts/arm
1º Endpoint: PFS at 24 weeks
Arm 1
mal-IRI + 5-FU/LV
+ oxaliplatin
Arm 2
mal-IRI + 5-FU/LV
Arm 3
nab-Pac + Gem
Control

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/047727

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/436 A61K9/127 A61K31/282 A61K31/4745 A61K31/475
A61K31/513 A61K31/519 A61P35/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHANG T C ET AL: "Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER VERLAG, BERLIN, vol. 75, no. 3, 11 January 2015 (2015-01-11), pages 579-586, XP035456963, ISSN: 0344-5704, DOI: 10.1007/S00280-014-2671-X [retrieved on 2015-01-11] the whole document ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2016	16/11/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Engl, Brigitte

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L. Chen, H. Shiah, T. Chao, R. K. Hsieh, G. Chen, J. Chang, G. Yeh: "Phase I study of liposome irinotecan (PEP02) in combination with weekly infusion of 5-FU/LV in advanced solid tumors", Journal of Clinical Oncology, vol. 28, no. 15_Suppl., E13024, 2010, XP002763720, DOI: 10.1200/jco.2010.28.15_suppl.e13024 Retrieved from the Internet: URL:http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.e13024 [retrieved on 2016-11-02] abstract -----	1-15
Y	KO A H ET AL: "A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer", BRITISH JOURNAL OF CANCER 20 AUG 2013, vol. 109, no. 4, 20 August 2013 (2013-08-20), pages 920-925, XP002763721, ISSN: 1532-1827 page 920, left-hand column, line 1 - page 921, left-hand column, line 43 page 923, right-hand column, line 12 - page 924, left-hand column, line 67 -----	1-15
Y	PETER J HOSEIN ET AL: "A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma", BMC CANCER, BIOMED CENTRAL, LONDON, GB, vol. 12, no. 1, 29 May 2012 (2012-05-29), page 199, XP021126474, ISSN: 1471-2407, DOI: 10.1186/1471-2407-12-199 the whole document -----	1-15

1

ASCO 2008

Phase I Study of Liposome Encapsulated Irinotecan (PEP02) in Advanced Solid Tumor Patients

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National Health Research Institutes, Tainan, Taiwan[1]; Chang Gung Memorial Hospital Linkou Medical Center, Taoyuan, Taiwan[2]; National Taiwan University Hospital, Taipei, Taiwan[3]; PharmaEngine, Inc., Taipei, Taiwan[4]

Abstract:

Background: PEP02 is a novel nanoparticle liposome formulation of irinotecan aiming to enhance tumor localization and improve pharmacokinetic properties of irinotecan and its active metabolite-SN38. The aims of the study are to define the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and pharmacokinetics (PK) of PEP02 in patients with advanced refractory solid tumors.

Methods: Pts with advanced refractory solid tumors, ECOG PS 0-1, and adequate hematological, hepatic and renal functions were eligible. PEP02 was given as 90 mins i.v. infusion, repeated every 3 weeks. The doses would have been escalated from 60, 120, 180 to 240 mg/m^2 in a single-patient cohort accelerated titration design. PK samples were collected on days 1, 2, 3, 8 and 21.

Results: A total of 11 pts (M/F 1/10, median age 47, range 41-67) were enrolled onto three dose levels, with 1, 6 and 4 pts at dose level I (60 mg/m^2), II (120 mg/m^2) and III (180 mg/m^2), respectively. DLT was observed in 3 pts, including 1 at dose level II (grade 3 catheter-related infection) and 2 at dose level III (grade 3 diarrhea and febrile neutropenia in 1 and grade 4 leucopenia and neutropenia in 1). MTD was determined as 120 mg/m^2. The PK of total irinotecan after PEP02 dosing were characterized by, i.e. after 120 mg/m^2, low clearance (mean = 0.0591 L/m^2/hr), small volume of distribution (mean = 1.8 L/m^2, similar to plasma volume), and prolonged terminal half-life (mean = 29.5 hr). The plasma concentration-time profiles of encapsulated irinotecan (PEP02) in each pt matched approximately with those of total irinotecan indicating that the release of irinotecan from liposomes occurred slowly over time. Comparing with published PK parameters after 125 mg/m^2 of irinotecan, the C_{max} of SN-38 after 120 mg/m^2 of PEP02 was lower (9.2 ± 3.5 vs 26.3 ± 11.9 ng/mL), the terminal $t_{1/2}$ of SN-38 was longer (75.4 ± 43.8 vs 10.4 ± 3.1 hrs) and the AUC of SN-38 was larger (710 ± 395 vs 229 ± 108 ng.h/mL). The best response of 10 evaluable pts was PR in 2 (cervical and pancreatic cancer) and SD in 3.

Conclusions: The MTD of PEP02 monotherapy at 3-week interval is 120 mg/m^2, which will be the recommended dose for future phase II studies. Preliminary data suggest that PEP02 exhibits encouraging pharmacokinetic, safety and efficacy profiles.

INTRODUCTION

- PEP02 is irinotecan hydrochloride (also known as CPT-11) encapsulated in a liposome drug delivery system (Hermes Biosciences, Inc.). CPT-11 is a topoisomerase I inhibitor which is currently on the markets worldwide to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

- Preclinical *in vivo* efficacy data in human breast carcinoma BT-474M1, gastric cancer MKN45, colon cancer HT-29, cervical cancer SiHa, brain tumor U87, and pancreatic cancer L3.6pl nude or SCID mouse models showed a clear indication of the improved efficacy of PEP02 over unencapsulated CPT-11 in terms of tumor regression without adversely increasing its toxicity.
- The results of the pharmacokinetic studies in rats and dogs clearly indicate that PEP02 not only increased plasma concentrations of CPT-11, but also prolonged its circulation in the blood.
- In toxicology studies, mice and rats showed better tolerability to PEP02 than to CPT-11, and dogs showed similar tolerability to both drugs despite much greater systemic exposure to SN-38 (active metabolite of CPT-11) in PEP02 dosed dogs. There was no accumulation of CPT-11 or SN-38 in the plasma from rats or dogs with repeat dosing. The target organs were mainly bone marrow and gastrointestinal tracts.

OBJECTIVES

- **Primary**
  - To evaluate the dose-limiting toxicity (DLT) and the toxicity profile of PEP02 in patients with advanced solid tumors
  - To determine the maximum tolerated dose (MTD) of PEP02
  - To characterize the pharmacokinetics of PEP02
- **Secondary**
  - To collect data for preliminary evaluation of tumor response

METHODS & PATIENTS

- **Study Design**
  - The accelerated titration design was used.
  - The initial dose given to the first patient was 60 mg/m^2.
  - Patients were planned to receive a minimum of 2 courses and a maximum of 6 courses, unless any withdrawal criteria occurred.

Escalation Decision Rule

No. of pts with DLT	Dose Level (mg/m^2)		
	60, 120 (1 pt)	180, 240 (2 pts)	300, 350, 400 (3 pts)
0	Proceed to next dose level	Proceed to next dose level	Proceed to next dose level
1	Enroll 5 more pts In the 5 pts • 0 DLT – proceed to next dose level • 1 or more DLT – dose escalation stopped	Enroll 4 more pts In the 4 pts • 0 DLT – proceed to next dose level • 1 or more DLT – dose escalation stopped	Enroll 3 more pts In the 3 pts • 0 DLT – proceed to next dose level • 1 or more DLT – dose escalation stopped
≥2	Not Applicable	Escalation stopped	Escalation stopped

- **Key Inclusion Criteria**
  - Histologically confirmed solid tumors, who have failed to standard or no established therapy exists, with at least one prior chemotherapy for advanced disease
  - ECOG of 0 or 1
  - Normal blood count and blood chemistry
- **Key Exclusion Criteria**
  - Prior treatment with irinotecan
  - Active CNS disorder or brain metastasis
  - Active or uncontrolled infection, cardiovascular disease

- **Dose-Limiting Toxicity was defined as the toxicities which were developed during the 1st treatment course including:**
  - G4 hematological toxicity lasting for longer than 3 days
  - Febrile neutropenia
  - G3 or greater non-hematological toxicity (except G3 nausea and vomiting)

RESULTS

- Between January 2005 and August 2005, 11 patients with histologically confirmed solid tumors were enrolled.
- Patient characteristics are showed in Table 1.

Table 1 Summary of Treated Patients

Dose level	Gander	Age	Tumor type	Course Received	Best Response
60 mg/m^2	F	60	Cervix	3	PD
120 mg/m^2	F	55	Cervix	2	PD
	F	58	Cervix	5	PR
	F	45	Squamous Cell Carcinoma of Lung	1	NE*
	F	46	Breast	2	PD
	F	41	Breast	4	SD
	F	43	Neurcendocrine	6	SD
180 mg/m^2	F	45	Cervix	4	PD
	F	47	Thymoma	6	SD
	M	59	Pancreas Head	6	PR
	F	67	Pancreas	1	PD

*Pt was withdrawn from the study without objective response evaluation due to treatment delay caused by catheter-related infection. However, PR was assessed after another 5 courses outside the study.

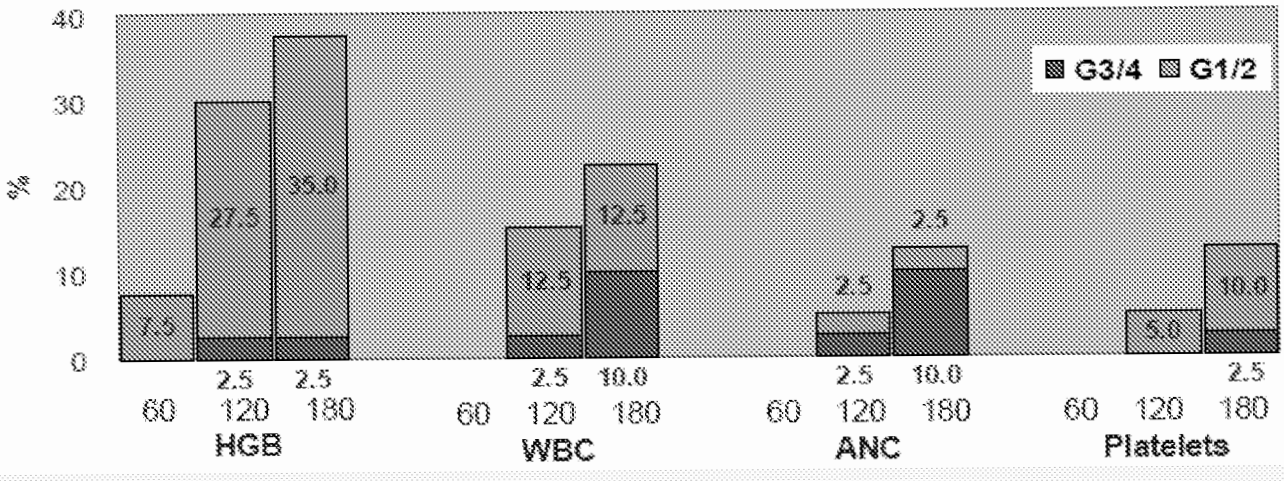
- **MTD and DLT**
  - The MTD was defined as the highest dose level which $\leq$ 1 out of six patients experienced DLT.
  - Among the 6 patients at 120 mg/m^2 dose level, only one patient experienced a DLT. Therefore, 120 mg/m^2 was determined as MTD.

Table 2 Summary of Dose Escalation and DLT

Order	Pt No.	Dose Level	DLT	DLT Type
1	101	60 mg/m^2	No	
2	102	120 mg/m^2	No	
3	201	180 mg/m^2	No	
4	103	180 mg/m^2	Yes	Grade 4 Leucopenia Grade 4 Neutropenia
5	202	180 mg/m^2	No	
6	203	180 mg/m^2	Yes	Grade 3 Diarrhea Grade 3 Febrile Neutropenia
7	205	120 mg/m^2	Yes	Grade 3 Infection (catheter- related)
8	206	120 mg/m^2	No	
9	301	120 mg/m^2	No	
10	104	120 mg/m^2	No	
11	207	120 mg/m^2	No	

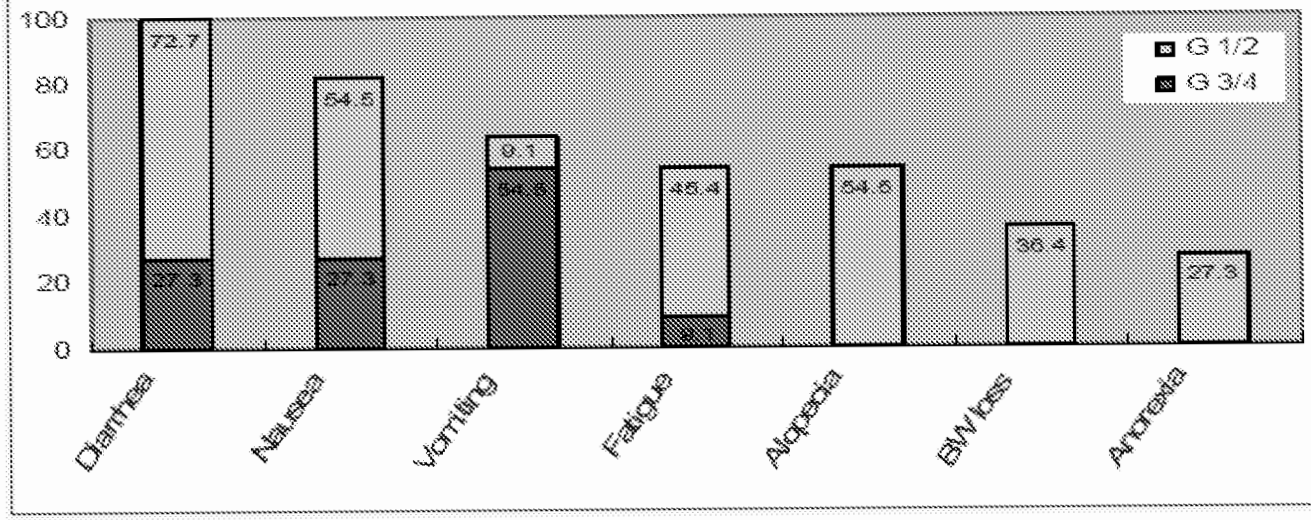
- **Safety results**
  - The hematology AEs were summarized in Fig 1.

Fig 1. Hematology AE by CTC grade by course
Total 40 courses were given to 11 patients



- The non-hematology AEs that experienced by at least 2 patients were summarized in Fig 2.

Fig 2. Non-Hematology Toxicities (%)



Pharmacokinetics results

- Comparing to the published data of CPT-11, C_{max} of PEP02 was higher, while C_{max} of SN-38 was lower; terminal $t_{1/2}$ of PEP02 and SN-38 were longer; and the AUC of PEP02 and SN-38 were larger in the PEP02 PK parameters.
- The Vd was small and approximately equal to the total plasma volume (~2 L/m^2), and the Cl was low (0.0591 L/m^2/hr).

- In addition, plasma concentrations of encapsulated irinotecan matched approximately with those of total irinotecan. These data indicate that most drugs were encapsulated in liposomes and slowly released into the circulation.

Table 3. Mean PK Parameters of Total CPT-11

Dose (mg/m^2)		C_{max} (μg/mL)	$t_{1/2}$ (hr)	AUC_{0-last} (hr·μg/mL)	$AUC_{0-\infty}$ (hr·μg/mL)	Cl (L/hr/m^2)	V_{ss} (L/m^2)	$MRT_{0-\infty}$ (hr)
120 (N=6)	Mean	79.4	29.5	2,835	2,963	0.0591	1.8	38.6
	SD	13.9	17.2	1,817	1,947	0.0367	0.771	19.5
	CV%	17.5	58.2	64.1	64.7	62.1	42.9	50.5

Table 4. Mean PK Parameters of Encapsulated CPT-11

Dose (mg/m^2)		C_{max} (μg/mL)	$t_{1/2}$ (hr)	AUC_{0-last} (hr·μg/mL)	$AUC_{0-\infty}$ (hr·μg/mL)	Cl (L/hr/m^2)	V_{ss} (L/m^2)	$MRT_{0-\infty}$ (hr)
120 (N=6)	Mean	72	31.1	2,601	2,787	0.0628	1.93	39.3
	SD	8.87	15.4	1,645	1,700	0.0405	0.786	19.1
	CV%	12.3	49.1	63.2	63.5	64.5	40.8	48.5

Table 5. Mean PK Parameters of SN-38

Dose (mg/m^2)		C_{max} (ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	AUC_{0-last} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	$MRT_{0-\infty}$ (hr)
120 (N=6)	Mean	9.20	75.4	21.9	710	997	109.0
	SD	3.50	43.8	26.3	395	680	54.4
	CV%	38.0	58.1	120	55.6	68.3	49.7

- **Preliminary efficacy data**
  - Definitions for tumor response was determined according to the RECIST criteria. The results of tumor response rate are summarized in Table 6.

Table 6. Tumor Response Rate (n = 10 evaluable patients)

Dose Level	CR	PR	SD	PD	ORR
60 mg/m^2 (n = 1)	0	0	0	1	0.0%
120 mg/m^2 (n = 5)	0	1	2	2	20.0%
180 mg/m^2 (n = 4)	0	1	1	2	25.0%
Total (n = 10)	0	2	3	5	20.0%

CONCLUSIONS

- The recommended dose of PEP02 is 120 mg/m^2 every 3 weeks when administered as a single agent.
- The most common toxicities are diarrhea and hematological toxicity, mostly grade 1 or 2.
- The safety, pharmacokinetic and efficacy profiles of CPT-11 have been ameliorated by this liposome formulation.
- PEP02 is justified for further clinical investigation.

Phase I Study of Liposome-Encapsulated Irinotecan (PEP02) in Advanced Solid Tumor Patients
Introduction
Methods
Results
Conclusions

PEPCOL: A randomized non-comparative phase II study to evaluate the efficacy and safety of PEP02 (MM-398) or irinotecan in combination with leucovorin and 5-fluorouracil as second-line treatment for patients with unresectable metastatic colorectal cancer. A GERCOR Study

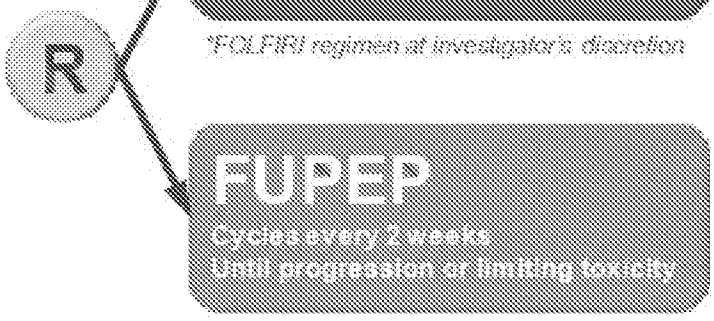
B. Chibaudel, F. Maindrault-Goebel, T. Andre, JB. Bachet, C. Louvet, A. Khalil, O. Dupuis, P. Hammel, ML. Garcia, M. Benhamoun, D. Brusquant, C. Arbaud, E. Wang, G. Yeh, F. Bonnetain, A. de Gramont

Institut Hospitalier Franco-Britannique, Levallois-Perret (France) ; Hôpital Saint-Antoine, Paris (France) ; Hôpital La Pitié-Salpetrière, Paris (France) ; Institut Mutualiste Montsouris, Paris (France) ; Hôpital Tenon, Paris (France) ; Clinique Victor Hugo, Le Mans (France) ; Hopital Beaujon, Clichy (France) ; Hôpital du Besançon, Besançon (France) ; Taipei (Taiwan)

Background

- PEP02 (MM-398) is a highly stable nanoliposomal irinotecan.
- The liposome formulation may reduce the toxicity of the encapsulated agent to healthy tissue while maintaining or increasing its antitumor potency, and theoretically has therapeutic advantages over free-form irinotecan such as site-specific delivery and extended release of drug.
- PEP02 has showed significantly superior efficacy to conventional irinotecan[1]:
  - *Magnitude of tumor inhibition 3-10 fold better at the same dose,*
  - *Lower C_{max} and longer elimination half-life,*
  - *Enhanced the total exposure ($AUC_{0-\infty}$) of SN-38,*
  - *Smaller volume of distribution,*
  - *Slower plasma clearance of total irinotecan.*
- The longer half-life of PEP02 over irinotecan may potentiate the effect of 5-fluorouracil (5FU), mimicking the FOLFIRI-3 regimen with a single daily infusion per cycle instead of 2-day infusion in the FOLFIRI-3 regimen[2,3].
- Trial registration: EudraCT 2010-020468-39A; NCT01375816.

Design



FOLFIRI-1*
-Folinic acid, 400mg/m²/2h (d1)
-Irinotecan, 180mg/m²/1h (d1)
-5FU bolus, 400mg/m² (d1)
-5FU infusion, 2400mg/m²/46h (d1-2)

Modified FOLFIRI-3*
-Folinic acid, 400mg/m²/2h (d1)
-Irinotecan, 90mg/m²/1h (d1)
-5FU infusion, 2400mg/m²/46h (d1-2)
-Irinotecan, 90mg/m² (d3)

FUPEP
-Folinic acid, 400mg/m²/2h (d1)
-PEP02, 80mg/m²/1h (d1)
-5FU infusion, 2400mg/m²/46h (d1-2)

- Non-comparative randomized phase II study,
- Randomization: minimization technique, stratified by:
  - Center,
  - GERCOR prognostic model (ECOG performance status [PS], lactate dehydrogenase LDH level)[1],
  - Time to progression of first-line (<9 vs. >9 months).

Material and Methods

MAIN INCLUSION CRITERIA

- Histologically proven colorectal adenocarcinoma,
- Measurable (RECIST 1.1) and unresectable metastatic disease,
- Failure of prior oxaliplatin-based first-line therapy,
- Age 18-75 years, WHO PS 0-2, baseline diarrhea grade ≤1,
- Total bilirubin <1.5 x UNL,
- Signed informed consent.

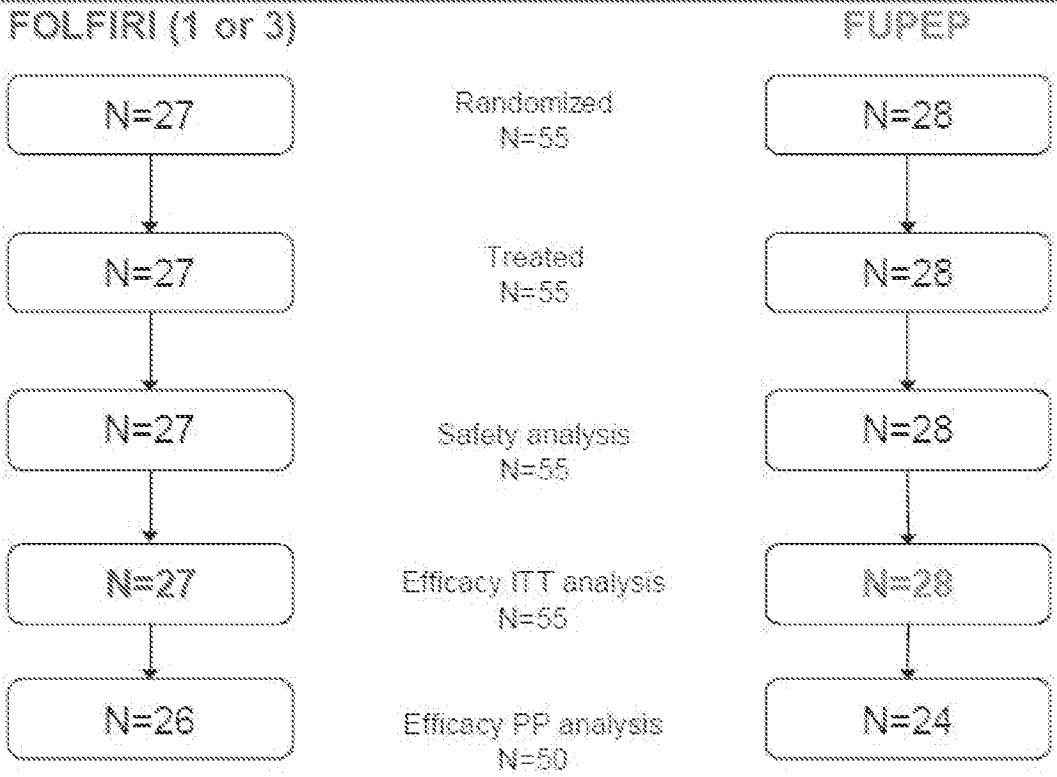
ENDPOINTS

- **Primary endpoint: Objective Response Rate (ORR).**
- Main secondary endpoints: progression-free survival (PFS), overall survival (OS), toxicity (CTCAE 4.0), quality of life (EQ-5D, QLQ-C30).

SAMPLE SIZE

- Simon's two-stage design: one-sided test α = 10%; power 90%,
- H0: 2-month ORR = 10%; H1: 2-month ORR = 25%
  - Simon's stage #1: N=54 – Move to stage 2 if ≥3 complete response (CR) or partial response (PR) at 2 months,
  - Simon's stage #2: N=26 – Interesting if ≥7 CR or PR at 2 months.

Flow-chart



- Enrollment: from May 2011 to August 2013.
- 6 active centers (France).

Results

Patient characteristics	FOLFIRI (N=27), %	FUPEP (N=28), %
Age ≥70	18.5	21.4
Male	51.8	67.9
First-line PFS <9 months	48.1	50.0
Prior use of bevacizumab	76.9	88.9
Prior oxaliplatin reintroduction	50.0	42.9
Single metastatic site	44.4	42.9
ECOG PS 0	55.6	35.7
Alkaline Phosphatase >3 x ULN	11.1	25.0
LDH >1 x ULN	59.3	65.4
Treatment exposure		
Chemotherapy regimen		
FOLFIRI-1	37.0	-
mFOLFIRI-3	63.0	-
Bevacizumab	46.4	42.8
No of cycles, N (mean)	268 (7.0)	226 (6.6)
Dose reduction	12.3	9.3

Response rate

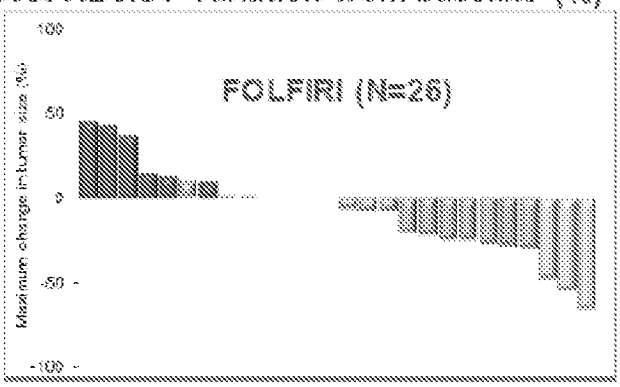
Early objective response rate (EOTR, 2-month ORR) – Simon's Stage #1 (N=54)

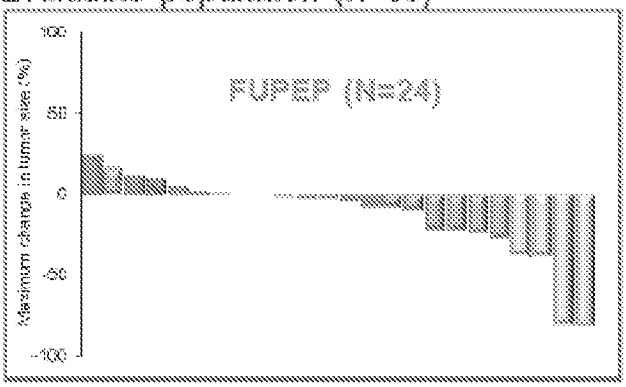
FOLFIRI arm: 2/27 (7.4%) FUPEP arm: 3/27 (11.1%)

Best ORR (ITT, N=55)

	FOLFIRI (N=27)			FUPEP (N=28)		
	N	%	95% CI	N	%	95% CI
CR	0	0.0	0.0-0.0	0	0.0	0.0-0.0
PR	3	11.1	-0.7-23.0	4	14.3	1.3-27.2
SD	17	63.0	44.8-81.2	13	46.4	28.0-64.9
PD	6	22.2	6.5-37.9	7	25.0	9.0-41.0
NE	1	3.7	-3.4-10.8	4	14.3	1.3-27.2
ORR	**3**	**11.1**	**-0.7-23.0**	**4**	**14.3**	**1.3-27.2**
DCR	20	74.1	57.5-90.6	17	60.7	42.6-78.8

Best RECIST variation from baseline (%) – Evaluable population (N=50)





Survivals

	FOLFIRI (N=27)	FUPEP (N=28)
PFS, median (95% CI)	6.8 (3.7-8.1)	5.0 (2.8-12.3)
OS, median (95% CI)	10.5 (6.9-21.1)	14.6 (8.0-16.5)

Safety

Grade 3-4 toxicity (%)	FOLFIRI (N=27)	FUPEP (N=28)
Neutropenia	29.6	10.7
Nausea	7.4	3.6
Vomiting	3.7	3.6
Diarrhea	33.3	21.4
Stomatitis	11.1	10.7
Alopecia (G2)	25.9	25.0

Conclusions

- This is the first randomized study evaluating the effect of adding PEP02 to leucovorin/5FU when administered to patients with metastatic colorectal cancer after failure of an oxaliplatin-based first-line therapy.
- The ORR (primary endpoint) of the FUPEP regimen was 14% (4/28), which compared favourably with FOLFIRI-1 (0/10, 0%) and was similar to the modified FOLFIRI-3 regimen (3/17, 18%).
- The incidence of neutropenia and diarrhea was lower in the FUPEP arm than in the FOLFIRI arm (11% and 21% vs. 30% and 33%). Other grade 3-4 toxicities were similar.
- Although the threshold of 2-month ORR ≥3 CR or PR was reached in the FUPEP arm, GERCOR decided not to move to the stage #2 of the study in order to optimize the FUPEP regimen.

References

[1] Drummond DC et al., Cancer Res 2006; 66:3271-3277
[2] Mabro M. et al., BJC 2006; 94:1287-92
[3] Bidard FC. et al., Ann Oncol 2009; 20:1042-7
[4] Chibaudel B. et al., Oncologist 2011; 16:1228-38

PEPCOL: A randomized, open-label, phase II study to evaluate the efficacy and safety of PEP02 (MK-2870) in combination with folfirinox and bevacizumab as second-line treatment for patients with unresectable, locally advanced or metastatic pancreatic cancer

GERCOR

Background

Methods

Results

Conclusion

References

Trial record 4 of 9 for: PEP02
Previous Study | Return to List | Next Study

Study of PEP02 as a Second Line Therapy for Metastatic Pancreatic Cancer

This study has been completed.

Sponsor:
PharmaEngine

Information provided by (Responsible Party):
PharmaEngine

ClinicalTrials.gov Identifier:
NCT00813163

First received: December 18, 2008
Last updated: January 12, 2015
Last verified: January 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The purpose of this study is to see the effect of **PEP02** in the treatment of metastatic pancreatic cancer.

Condition	Intervention	Phase
Pancreatic Neoplasms	Drug: **PEP02**	Phase 2

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase II Study of **PEP02** as a Second Line Therapy for Patients With Metastatic Pancreatic Cancer

Resource links provided by NLM:

MedlinePlus related topics: Cancer Pancreatic Cancer

Drug Information available for: Irinotecan

U.S. FDA Resources

Further study details as provided by PharmaEngine:

Primary Outcome Measures:

- Survival Rate [Time Frame: 3-month] [Designated as safety issue: No]

Secondary Outcome Measures:

- other efficacy endpoints such as objective tumor response, PFS, duration of response, overall survival, tumor marker response of CA19-9, clinical benefit response [Designated as safety issue: No]
- toxicities [Designated as safety issue: Yes]
- pharmacogenetics [Designated as safety issue: No]

Enrollment: 41
Study Start Date: January 2009
Study Completion Date: July 2012
Primary Completion Date: December 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: **PEP02** Liposome Irinotecan	Drug: **PEP02** 120 mg/m2, IV infusion for 90 minutes on day 1 of each 21 days as a treatment cycle. Number of Cycles: until progression or unacceptable toxicity develops. Other Name: Liposome irinotecan

Detailed Description:

Gemcitabine monotherapy or a gemcitabine-based combination regimen is the standard first line therapy for advanced pancreatic cancer. After disease progression, there is no standard treatment available. In animal studies and a previous phase I trial, PEP02 has shown anti-tumor activity and preliminary efficacy in pancreatic cancer. In addition, a phase II study of free-form irinotecan single agent has already shown encouraging activity as second-line treatment for patients with advanced pancreatic cancer refractory to gemcitabine. The liposome formulation of PEP02 theoretically has therapeutic advantages over free-form irinotecan, such as site-specific delivery and extended release of drug. Hence PEP02 may be able to provide better efficacy than free-form irinotecan.

The primary purpose of this phase II study is to evaluate the activity of PEP02 as a second-line therapy in patients with metastatic pancreatic cancer failed to gemcitabine treatment. The primary goal is to measure the 3-month survival rate. An optimal Simon's 2-stage design will be used for this exploratory phase II study.

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
- Metastatic disease
- Documented disease progression after treatment with 1 line of prior gemcitabine-based regimen
- Karnofsky performance status equal or more than 70

Exclusion Criteria:

- With active CNS metastases
- With clinically significant gastrointestinal disorder (e.g., bleeding, inflammation, occlusion, or diarrhea > grade 1)
- Major surgery or radiotherapy within 4 weeks
- Prior participation in any investigational drug study within 4 weeks
- With prior irinotecan treatment

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00813163

Locations

United States, California

Comprehensive Cancer Center, UCSF
San Francisco, California, United States, 94115

Taiwan

National Health Research Institutes/National Chen-Kung University Hospital
Tainan, Taiwan, 704

National Taiwan University Hospital
Taipei, Taiwan, 100

Sponsors and Collaborators

PharmaEngine

Investigators

Principal Investigator:	Li-Tzong Chen, M.D.	National Health Research Institutes, Taiwan
Principal Investigator:	Andrew H Ko, M.D.	University of California, San Francisco
Principal Investigator:	Yu-Lin Lin, M.D.	National Taiwan University Hospital

More Information

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Ko AH, Tempero MA, Shan YS, Su WC, Lin YL, Dito E, Ong A, Wang YW, Yeh CG, Chen LT. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. Br J Cancer. 2013 Aug 20;109 (4):920-5. doi: 10.1038/bjc.2013.408. Epub 2013 Jul 23.

Responsible Party:	PharmaEngine
ClinicalTrials.gov Identifier:	NCT00813163 History of Changes
Other Study ID Numbers:	PEP0208
Study First Received:	December 18, 2008
Last Updated:	January 12, 2015
Health Authority:	United States: Food and Drug Administration Taiwan: Department of Health

Keywords provided by PharmaEngine:
Phase II study
Second line
Pancreatic cancer
Metastatic

Additional relevant MeSH terms:

Pancreatic Neoplasms	Irinotecan
Digestive System Neoplasms	Antineoplastic Agents, Phytogenic
Neoplasms by Site	Antineoplastic Agents
Neoplasms	Topoisomerase I Inhibitors
Endocrine Gland Neoplasms	Topoisomerase Inhibitors
Digestive System Diseases	Enzyme Inhibitors
Pancreatic Diseases	Molecular Mechanisms of Pharmacological Action
Endocrine System Diseases	

ClinicalTrials.gov processed this record on October 07, 2016

View of NCT01359007 on 2011_05_23

ClinicalTrials Identifier: NCT01359007
Updated: 2011_05_23

Descriptive Information

Brief title FOLFIRINOX in Patients With Inoperable Pancreatic Cancer

Official title A Phase II Study Evaluating the Rate of R0 Resection (Microscopically Negative Margins) After Induction Therapy With 5- Fluorouracil, Leucovorin, Oxaliplatin, Irinotecan (FOLFIRINOX) in Patients With Borderline Resectable or Locally Advanced Inoperable Pancreatic Cancer.

Brief summary

The prognosis of patients with locally advanced unresectable pancreatic cancer is poor, and the median survival is less than 1 year. FOLFIRINOX therapy, which induces tumor downstaging sufficient to allow surgical resection, could improve the overall survival of patients with locally advanced pancreatic cancer. Based on the FOLFIRINOX regimen for advanced pancreatic cancer, a phase II study of this regimen in patients with locally advanced unresectable and borderline pancreatic cancer is planned to determine the rate of conversion to operability.

Detailed description

Phase Phase 2
Study type Interventional
Study design Treatment
Study design Open Label
Study design Single Group Assignment
Study design Safety/Efficacy Study
Primary outcome Measure: To estimate, among patients with locally advanced unresectable and borderline resectable pancreatic cancer, the proportion in whom R0 resection is achieved after neoadjuvant therapy.
Time Frame: 2 years
Safety Issue? No
Secondary outcome Measure: Proportion of patients whose pancreatic cancer is operable (resulting in R0 or R1 resection) following induction therapy.
Time Frame: 2 years
Safety Issue? No

Secondary outcome	Measure: Response rate (either CR or PR by RECIST 1.1 criteria) Time Frame: 2 years Safety Issue? No
Secondary outcome	Measure: Overall survival Time Frame: 2 years Safety Issue? No
Secondary outcome	Measure: 4. Toxicity (proportion of patients in whom any grade adverse events are observed) Time Frame: 2 years Safety Issue? Yes
Enrollment	25 (Anticipated)
Condition	Adenocarcinoma of Pancreas
Arm/Group	Arm Label: FOLFIRINOX Experimental Combination of drugs (Irinotecan, Oxaliplatin, Leucovorin, and 5-FU) known as FOLFIRINOX every 2 weeks for 4 treatments. At the end of 4 cycles, patients will be re-evaluated for resectability by CT scan within 28 days of the last dose of chemo. If found amendable to surgery, patient will proceed with resection, and type of resection (R0 or R1) will be recorded.
Intervention	Drug: Irinotecan, Oxaliplatin, Leucovorin, 5-FU Arm Label: FOLFIRINOX 5-FU 2400 mg/m2 IV continuous infusion for 46-48 hours Days 1-3 for 2 weeks 5-FU 400 mg/m2 IV Bolus Day 1 Oxaliplatin 85 mg/m2 IV over 120min +/-30 min. Day 1 Irinotecan 180 mg/m2 IV to run over 90 min +/- 30 min Day 1 Leucovorin (Before bolus 5-FU) 400 mg/m2 IV over 120 min. +/- 30 Day 1 May give oxaliplatin and leucovorin concurrently

Recruitment Information

Status	Not yet recruiting
Start date	2011-05
Last follow-up date	2013-05 (Anticipated)
Primary completion date	2013-05 (Anticipated)

Criteria

Inclusion Criteria:

- Histologically or cytologically confirmed locally advanced unresectable or borderline resectable adenocarcinoma of pancreas
- Patients must have measurable disease as defined by RECIST 1.1 RECIST evaluations must have occurred within 4 weeks prior to study entry

- No evidence of hepatic or pulmonary metastatic disease by CT or CT/PET scans
- Male or non-pregnant and non-lactating female age > or equal to 18 years and < or equal to 70 years of age
-Patient must have received no prior therapy for the treatment of locally advanced unresectable or borderline resectable pancreatic cancer
-Patients must have adequate blood counts at baseline and blood chemistry levels
-Patient has ECOG Performance Status 0 to 1

Exclusion Criteria:
- Patients with islet cell neoplasms excluded
-Patients with known brain metastases
- Therapeutic Coumadin for a history of pulmonary emboli or DVT
-Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
-Known infection with HIV, hepatitis B or hepatitis C
-Major surgery or vascular device placement within 4 weeks prior to Day 1 of treatment in study
- Prior chemotherapy or radiation for pancreatic cancer
- History of allergy or hypersensitivity to the study drugs
-Patient is enrolled in any other clinical protocol or investigational trial
-Metastatic disease on radiological staging
-Prior malignancy within last 3 years
-Significant cardiac disease
-Any prior GI disease or history of prior pelvic or abdominal radiation in which in opinion of the investigator may place the patient at increased risk
-peripheral sensory neuropathy > or equal to grade 2 at baseline

Gender	Both
Minimum age	18 Years
Maximum age	70 Years
Healthy volunteers	No

Administrative Data

Organization name	University of Oklahoma
Organization study ID	FOLFIRINOX
Sponsor	University of Oklahoma
Health Authority	United States: Institutional Review Board

View of NCT01359007 on 2015_05_28

ClinicalTrials Identifier: NCT01359007
Updated: 2015_05_28

Descriptive Information

Brief title FOLFIRINOX in Patients With Inoperable Pancreatic Cancer

Official title A Phase II Study Evaluating the Rate of R0 Resection (Microscopically Negative Margins) After Induction Therapy With 5- Fluorouracil, Leucovorin, Oxaliplatin, Irinotecan (FOLFIRINOX) in Patients With Borderline Resectable or Locally Advanced Inoperable Pancreatic Cancer.

Brief summary

The prognosis of patients with locally advanced unresectable pancreatic cancer is poor, and the median survival is less than 1 year. FOLFIRINOX therapy, which induces tumor downstaging sufficient to allow surgical resection, could improve the overall survival of patients with locally advanced pancreatic cancer. Based on the FOLFIRINOX regimen for advanced pancreatic cancer, a phase II study of this regimen in patients with locally advanced unresectable and borderline pancreatic cancer is planned to determine the rate of conversion to operability.

Detailed description

Phase Phase 2
Study type Interventional
Study design Treatment
Study design Open Label
Study design Single Group Assignment
Study design Safety/Efficacy Study
Primary outcome Measure: To estimate, among patients with locally advanced unresectable and borderline resectable pancreatic cancer, the proportion in whom R0 resection is achieved after neoadjuvant therapy.
Time Frame: 2 years
Safety Issue? No
Secondary outcome Measure: Proportion of patients whose pancreatic cancer is operable (resulting in R0 or R1 resection) following induction therapy.
Time Frame: 2 years
Safety Issue? No

Secondary outcome	Measure: Response rate (either Complete Response (CR) or Partial Response (PR) by RECIST 1.1 criteria) Time Frame: 2 years Safety Issue? No
Secondary outcome	Measure: Overall survival Time Frame: 2 years Safety Issue? No
Secondary outcome	Measure: 4. Toxicity (proportion of patients in whom any grade adverse events are observed) Time Frame: 2 years Safety Issue? Yes
Enrollment	5 (Actual)
Condition	Adenocarcinoma of Pancreas
Arm/Group	Arm Label: FOLFIRINOX Experimental Combination of drugs (Irinotecan, Oxaliplatin, Leucovorin, and 5-Fluorouracil (5-FU)) known as FOLFIRINOX every 2 weeks for 4 treatments. At the end of 4 cycles, patients will be re-evaluated for resectability by CT scan within 28 days of the last dose of chemo. If found amendable to surgery, patient will proceed with resection, and type of resection (R0 or R1) will be recorded.
Intervention	Drug: Irinotecan, Oxaliplatin, Leucovorin, 5-FU Arm Label: FOLFIRINOX 5-FU 2400 mg/m2 IV continuous infusion for 46-48 hours Days 1-3 for 2 weeks 5-FU 400 mg/m2 IV Bolus Day 1 Oxaliplatin 85 mg/m2 IV over 120min +/-30 min. Day 1 Irinotecan 180 mg/m2 IV to run over 90 min +/- 30 min Day 1 Leucovorin (Before bolus 5-FU) 400 mg/m2 IV over 120 min. +/- 30 Day 1 May give oxaliplatin and leucovorin concurrently

Recruitment Information

Status	Terminated
Start date	2011-05
Last follow-up date	2013-10 (Actual)
Primary completion date	2013-10 (Actual)

Criteria

Inclusion Criteria:
- Histologically or cytologically confirmed locally advanced unresectable or borderline resectable adenocarcinoma of pancreas
- Patients must have measurable disease as defined by RECIST 1.1 RECIST evaluations must have occurred within 4 weeks prior to study entry

- No evidence of hepatic or pulmonary metastatic disease by CT or CT/PET scans
- Male or non-pregnant and non-lactating female age > or equal to 18 years and < or equal to 70 years of age
-Patient must have received no prior therapy for the treatment of locally advanced unresectable or borderline resectable pancreatic cancer
-Patients must have adequate blood counts at baseline and blood chemistry levels
-Patient has ECOG Performance Status 0 to 1

Exclusion Criteria:
- Patients with islet cell neoplasms excluded
-Patients with known brain metastases
- Therapeutic Coumadin for a history of pulmonary emboli or deep vein thrombosis (DVT)
-Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
-Known infection with HIV, hepatitis B or hepatitis C
-Major surgery or vascular device placement within 4 weeks prior to Day 1 of treatment in study
- Prior chemotherapy or radiation for pancreatic cancer
- History of allergy or hypersensitivity to the study drugs
-Patient is enrolled in any other clinical protocol or investigational trial
-Metastatic disease on radiological staging
-Prior malignancy within last 3 years
-Significant cardiac disease
-Any prior gastrointestinal (GI) disease or history of prior pelvic or abdominal radiation in which in opinion of the investigator may place the patient at increased risk
-peripheral sensory neuropathy > or equal to grade 2 at baseline

Gender	Both
Minimum age	18 Years
Maximum age	70 Years
Healthy volunteers	No

Administrative Data

Organization name	University of Oklahoma
Organization study ID	1977
Sponsor	University of Oklahoma
Health Authority	United States: Institutional Review Board

View of NCT01446458 on 2011_10_04

ClinicalTrials Identifier: NCT01446458
Updated: 2011_10_04

Descriptive Information

Brief title Phase I Study of Stereotactic Body Radiation Therapy and FOLFIRINOX in the Neoadjuvant Therapy of Pancreatic Cancer

Official title Phase I Study of Stereotactic Body Radiation Therapy and 5-Fluorouracil, Oxaliplatin and Irinotecan (FOLFIRINOX) in the Neoadjuvant Therapy of Pancreatic Cancer

Brief summary

The purpose of this study is to determine whether using FOLFIRINOX chemotherapy and Stereotactic Body Radiation Therapy (SBRT) prior to surgery in patients with pancreatic cancer is safe and well tolerated. This study will obtain preliminary data on the response of the cancer to this therapy by Magnetic Resonance Imaging (MRI) and by studying the cancer after it is resected surgically.

In addition, the investigators will perform biochemical studies on the tumor tissue obtained from your tissue biopsy as well as from the tumor removed by the surgeon in order to measure the effect of treatment with FOLFIRINOX and SBRT on several proteins that may be important in the behavior of pancreatic cancer cells.

The data obtained from this trial will be extremely valuable to help improve the approach to treating pancreatic cancer in the future. If you do not undergo surgery after completion of FOLFIRINOX + SBRT, the investigators will request a second biopsy of the tumor under computer tomography (CT) -guidance in order to measure the effect of treatment on your tumor.

Detailed description

The current standard of care for treating early stage pancreatic cancer involves surgery followed by chemotherapy and chemoradiotherapy using conventional fractionated external beam radiation therapy (EBRT). Despite the use of this standard treatment, the outcome for patients whose pancreatic cancers have been surgically removed remains poor. Patients with more advanced pancreatic cancers may experience even more inferior outcomes due to the difficulty to resect the cancer completely. In this particular group of patients, chemotherapy and radiation are offered to improve the resectability of the cancer.

Traditional chemotherapy used in the treatment of pancreatic cancer has

included drugs such as gemcitabine. Recently, a chemotherapy regimen called Folfirinox has been used in the treatment of advanced pancreatic cancer. Fofirinox is also associated with improved outcomes when compared to gemcitabine in this particular group of patients.

Stereotactic body radiotherapy (SBRT) uses a higher dose of radiation to the cancer, but the treatment lasts for a significantly shorter period of time compared to conventional radiation. SBRT has advantages over conventional radiation that include: shorter duration of therapy (one to three days versus two to five weeks) and the ability to deliver full doses of chemotherapy. Studies evaluating SBRT for patients with pancreatic cancer have shown that SBRT is as effective as conventional radiation with less toxicity. SBRT combined with chemotherapy has been very well tolerated in patients with pancreatic cancer.

This study will ask whether giving chemotherapy with Folfirinox followed in short sequence by radiation therapy using a modified type of radiation, called Stereotactic Body Radiation Therapy (SBRT), is a feasible and safe approach. Also the investigators would like to see if this approach can improve the outcomes of patients who may undergo surgery for their pancreatic cancer.

Phase	Phase 1
Study type	Interventional
Study design	Treatment
Study design	Open Label
Study design	Single Group Assignment
Primary outcome	Measure: Maximum tolerated total dose of stereotactic body radiation to patients with resectable or borderline resectable pancreas cancer following Folfirinox chemotherapy Time Frame: Four weeks Safety Issue? Yes Description: A standard 3 + 3 design will be used for evaluating the safety and tolerability of SBRT radiation doses. Any grade 3 liver, gastric, small bowel or spinal cord toxicity or any grade 4 toxicity (hematologic or other non-hematologic except for diarrhea) will be considered a dose limiting toxicity (DLT). Each cohort will consist of 3 patients, unless 1 of the patients experiences a DLT in which case the cohort will be expanded to 6 patients. The maximum tolerated dose (MTD) will be defined as the dose level below that which results in a DLT in 2 or more of the 6 patients in a cohort.
Secondary outcome	Measure: Clinical and pathologic objective response rate as measured by MRI (clinical response) and histopathology and rate of complete resection (R0) (pathologic response) Time Frame: ten weeks Safety Issue? No Description:

	The overall pathologic (complete + partial) response rate and margin negative resection rate will be estimated two ways: using all registered, and resected patients (via the ITT principle, for effectiveness assessment). The overall objective clinical response rate will involve MRI assessment of pancreas tumors of all registered patients with comparison of baseline MRI measurement to post-Folfirinox/post-SBRT measurement prior to surgical resection using RECIST criteria. Measurements will involve all registered patients.
Enrollment	24 (Anticipated)
Condition	Cancer of Pancreas
Condition	Cancer of the Pancreas
Condition	Neoplasms, Pancreatic
Condition	Pancreas Cancer
Condition	Pancreas Neoplasms
Intervention	Drug: Folfirinox Chemotherapy for 4 cycles (1 cycle = 15 days):Oxaliplatin 85 mg/m2 day 1 every 15 days; Irinotecan 180 mg/m2 day 1 every 15 days; Leucovorin 400 mg/m2 day 1 every 15 days; 5-Fluorouracil infusion 2400 mg/m2 IV continuous infusion over 46 hours (+/- 2 hours) day 1 every 15 days; pegylated filgrastim (neulasta) 6 mg SC intramuscular injection once every 15 days, given on day 4 of chemotherapy
Intervention	Radiation: Stereotactic Body Radiotherapy (SBRT) Stereotactic Body Radiotherapy: Begins 2 weeks after completion of final cycle of Folfirinox chemotherapy. Initial Dose Level 1 cohort: 10 Gy SBRT to primary tumor volume (PTV) and 2 Gy SBRT to retroperitoneal margin on days 1, 2, and 3. Total Gy to Gross tumor volume (GTV) is 36 Gy. Toxicity Assessment will occur weekly for 4 weeks.

Recruitment Information

Status	Not yet recruiting
Start date	2011-10
Last follow-up date	2013-12 (Anticipated)
Primary completion date	2013-04 (Anticipated)

Criteria

Inclusion Criteria:

- Patients must have histologic or cytologic diagnosis of pancreatic adenocarcinoma with radiological resectable or borderline resectable disease as

determined by an experienced surgical oncologist (Dr Shishir Maithel).

- Patients must be 21 years or older.

- Patients must not have received prior chemotherapy or radiation for pancreatic cancer.

- Patients must have performance status of 0-1 on the ECOG (Eastern Oncology Group) scale (Appendix II).

- Patients must have adequate bone marrow function: absolute neutrophil count >1,500/cmm, platelet count >100,000/cmm.

- Patients must be informed of the investigational nature of this study and must give written informed consent prior to the receiving of treatment per this protocol.

Exclusion Criteria

- Patients with endocrine tumors or lymphoma of the pancreas.

- Patients whose tumor is less than 3 mm from the duodenum as measured by either CT or MRI

- History of central nervous system (CNS) metastases.

- Liver dysfunction, bilirubin > 1.5 mg/dL; aspartate transaminase (AST) and alanine amino transferase (ALT) > 1.5 times upper limit of institutional normal.

- Creatinine ≥ 1.5 mg/dL

- Albumin < 2.5 g/dL.

- INR ≥ 1.5 (in the absence of ongoing treatment with warfarin).

- Breast feeding.

- Serious active infection.

- Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator).

- Active second primary malignancy (except in situ carcinoma of the cervix, or adequately treated basal cell carcinoma of the skin) within less than one year of enrollment into this study.

Gender	Both
Minimum age	18 Years
Healthy volunteers	No

Administrative Data

Organization name	Emory University
Organization study ID	WCI1998-11
Sponsor	Emory University
Health Authority	United States: Institutional Review Board

View of NCT01494506 on 2013_08_01

ClinicalTrials Identifier: NCT01494506
Updated: 2013_08_01

Descriptive Information

Brief title Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer

Official title A Randomized, Open Label Phase 3 Study of MM-398, With or Without 5-Fluorouracil and Leucovorin, Versus 5 Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer Who Have Failed Prior Gemcitabine-based Therapy

Brief summary

The study is an open label, randomized phase 3 study of MM-398 with or without 5-Fluorouracil (5-FU) and Leucovorin (also known as folinic acid), versus 5-FU and leucovorin in metastatic pancreatic cancer patients who have progressed on prior gemcitabine based therapy.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Open Label
Study design	Parallel Assignment
Study design	Efficacy Study
Primary outcome	Measure: Overall Survival Time Frame: 24 months Safety Issue? No
Secondary outcome	Measure: Progression Free Survival Time Frame: 24 months Safety Issue? No
Secondary outcome	Measure: Time to treatment failure Time Frame: 24 months Safety Issue? No
Secondary outcome	Measure: Objective response rate Time Frame: 24 months Safety Issue? No

Enrollment	405 (Anticipated)
Condition	Metastatic Pancreatic Cancer
Arm/Group	Arm Label: MM-398 Experimental MM-398 Q3W IV
Arm/Group	Arm Label: 5 Fluorouracil and Leucovorin IV Active Comparator 5 Fluorouracil and Leucovorin IV
Arm/Group	Arm Label: MM-398, 5-FU and Leucovorin Experimental MM-398, 5-FU and Leucovorin Q2W IV
Intervention	Drug: MM-398 Arm Label: MM-398 Arm A: MM-398 120 mg/m2 IV Q3W Arm C: MM-398 80mg/m2 IV Q2W
Intervention	Drug: 5 Fluorouracil Arm Label: 5 Fluorouracil and Leucovorin IV Arm B: 5 Fluorouracil 2000 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: 5 Fluorouracil 2400 mg/m2 IV every 2 weeks
Intervention	Drug: Leucovorin Arm Label: 5 Fluorouracil and Leucovorin IV Arm B: Leucovorin 200 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: Leucovorin 400 mg/m2 IV every 2 weeks

Recruitment Information

Status	Recruiting
Start date	2011-11
Last follow-up date	2014-06 (Anticipated)
Primary completion date	2013-12 (Anticipated)

Criteria

Inclusion Criteria:
- Histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas
- Metastatic disease
- Documented disease progression after prior gemcitabine based therapy
- KPS >/= 70
- Adequate bone marrow function

- Adequate hepatic function
- Adequate renal function

Exclusion Criteria:
- Active CNS metastasis
- Clinically significant GI disorders
- Severe arterial thromboembolic events less than 6 months before inclusion
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
- Active infection or uncontrolled fever
- Pregnant or breast feeding patients

Gender	Both
Minimum age	18 Years
Healthy volunteers	No

Administrative Data

Organization name	Merrimack Pharmaceuticals
Organization study ID	MM-398-07-03-01
Sponsor	Merrimack Pharmaceuticals
Health Authority	United States: Food and Drug Administration

Trial record 6 of 9 for: PEP02
Previous Study | Return to List | Next Study

Study of MM-398 With or Without 5-FU/LV, Versus 5-FU/LV in Patients With Metastatic Pancreatic Cancer (NAPOLI-1)

This study has been completed.

Sponsor:
Merrimack Pharmaceuticals

Information provided by (Responsible Party):
Merrimack Pharmaceuticals

ClinicalTrials.gov Identifier:
NCT01494506

First received: December 14, 2011
Last updated: June 16, 2016
Last verified: June 2016
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Purpose

The study is an open label, randomized phase 3 study of MM-398 with or without 5-Fluorouracil (5-FU) and Leucovorin (also known as folinic acid), versus 5-FU and leucovorin in metastatic pancreatic cancer patients who have progressed on prior gemcitabine based therapy.

Condition	Intervention	Phase
Metastatic Pancreatic Cancer	Drug: MM-398 Drug: 5 Fluorouracil Drug: Leucovorin	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Randomized, Open Label Phase 3 Study of MM-398, With or Without 5-Fluorouracil and Leucovorin, Versus 5 Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer Who Have Failed Prior Gemcitabine-based Therapy

Resource links provided by NLM:

MedlinePlus related topics: Cancer Pancreatic Cancer

Drug Information available for: Fluorouracil Gemcitabine

U.S. FDA Resources

Further study details as provided by Merrimack Pharmaceuticals:

Primary Outcome Measures:

- Overall Survival [Time Frame: From randomization to death; until the data cut off 14 Feb 2014. The maximum time in follow up was 25 months.] [Designated as safety issue: No]

  Overall survival was the primary efficacy endpoint of the study and was defined as the time from the date of patient randomization to the date of death or the date the patient was last known to be alive. OS was summarized by Kaplan-Meier methodology for each treatment group. Pairwise treatment group comparisons were carried out using unstratified log rank analyses on the ITT population. Hazard ratio estimates are from Cox regression analysis. The comparison of Arm C is based only on patients who were randomized under the 3-arm version of the protocol. Consequently, the 5-FU+Leucovorin (Combo Therapy Comparison) group is a subset of all patients randomized to 5-FU+Leucovorin, which is the Mono Therapy Comparison control and contains patients randomized under both the 2-arm and 3-arm versions of the protocol.

Secondary Outcome Measures:

- Progression Free Survival [Time Frame: Randomization until disease progression or death from any cause; Until the data cut off of 14 Feb 2014. The maximum time in follow up was 25 months.] [Designated as safety issue: No]

  Progression-free survival was defined as the time from the date of randomization to the date of disease progression, or death (any cause) on or prior to the clinical cutoff date, whichever occurred earlier. Participants who did not have disease progression or had not died were censored at the date of the last tumor assessment. Patients with two or more consecutive missing response assessments prior to a visit with documented progression (or death) were censored at the last date of tumor assessment when the patient was documented to be progression free. PFS was summarized using Kaplan-Meier methods. The comparison of Arm C is based only on patients who were randomized under the 3-arm version of the protocol. Consequently, the 5-FU+Leucovorin (Combo Therapy Comparison) group is a subset of all patients randomized to 5-FU+Leucovorin, which is the Mono Therapy Comparison control and contains patients randomized under both the 2-arm and 3-arm versions of the protocol.

- Objective Response Rate [Time Frame: Assessment every 6 weeks after initial response; Day 1 to data cut off of 14 Feb 2014; maximum time on study 25 months.] [Designated as safety issue: No]

  The objective response rate was a secondary efficacy endpoint of the study and was defined by the percentage of patients in the study population with a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by the investigator. Best overall response was defined per RECIST (version 1.1) recorded from randomization until progression or end of study. RECIST (v 1.1) criteria does not require confirmation of response, but an additional, more stringent analysis was also conducted, with designation of CR (or PR) requiring confirmation of response at least 4 weeks following the initial assessment of CR (or PR). Stable disease (SD) required an assessment of SD at least 6 weeks after starting treatment. Subjects with insufficient data for response classification were classified as Not Evaluable for best overall response, and as a non-responder for objective response, in the ITT population. Treatment groups are as indicated for the primary outcome of OS.

- Time to Treatment Failure [Time Frame: Randomization to treatment discontinuation (any cause). The maximum time in follow up was 25 months] [Designated as safety issue: No]

  Time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity or death.

- Percentage of Patients With Clinical Benefit Response [Time Frame: Randomization to treatment discontinuation.The maximum time in follow up was 25 months] [Designated as safety issue: No]

  Composite measure based on patient-reported pain (per VAS), patient-reported pain medication, KPS, and weight. Clinical benefit is indicated by either: (a) improvement in pain (less pain intensity with stable or decreased pain medication; or less pain medication with stable or decreased pain intensity) with stable or improved KPS; or (b) improvement in KPS with stable or improved pain. With stable for KPS and pain, clinical benefit may be indicated with an observation of positive weight change. Clinical benefit response (CBR) was classified weekly and a patient was considered a clinical benefit responder if clinical benefit was observed and maintained over a 4 week period.

- Percentage of Patients With Tumor Marker (CA 19-9) Response [Time Frame: Baseline to treatment discontinuation every 6 weeks; The maximum time in follow up was 25 months] [Designated as safety issue: No]

  Tumor marker response (TMR) was evaluated by the change in CA19-9 serum levels. Response was defined as a decrease of 50% of CA19-9 in relation to the baseline level at least once during the treatment period.

- EORTC-QLQ-C30 [Time Frame: Baseline to treatment discontinuation every 6 weeks; The maximum time in follow up was 25 months] [Designated as safety issue: No]

  This patient recorded outcome consists of 15 subscales in 3 independent domains: global health-related quality of life (HRQoL), functional scales (cognitive, emotional, physical, role and social functioning), and symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain). For each subscale, patients were classified as improved, worsened or stable. Improvement is indicated by achievement of subscale score at least 10% improved from baseline and maintained for at least 6 weeks. Worsened is indicated by subscale score at least 10% worse than baseline. Stable is indicated by neither improvement nor worsened. Achievement of improvement prior to worsening was classified as improvement.

- Pharmacokinetic Measurements of Total Irinotecan [Time Frame: 6 weeks after first study drug administration] [Designated as safety issue: No]

  Plasma concentration-time data for MM-398 will be analyzed using population pharmacokinetic methods.

Enrollment:	417
Study Start Date:	November 2011
Study Completion Date:	October 2015
Primary Completion Date:	February 2014 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions

Experimental: MM-398 MM-398 120 mg/m2 Q3W IV. Note: The published dose of ONIVYDE was expressed as the irinotecan hydrochloride trihydrate until October 2015. It is now expressed as the irinotecan free base. Converting a dose based on irinotecan hydrochloride trihydrate to a dose based on irinotecan free base is accomplished by substituting the Molecular Weight of irinotecan hydrochloride trihydrate (677.19 g/mole) with the Molecular Weight of irinotecan free base (586.68 g/mole), which results in a conversion factor of 0.866. 120 mg/m2 dose of irinotecan hydrochloride trihydrate is equivalent to 100 mg/ m2 of irinotecan free base.	Drug: MM-398 Arm A: MM-398 120 mg/m2 IV Q3W Arm C: MM-398 80mg/m2 IV Q2W Other Name: **PEP02**
Active Comparator: 5 Fluorouracil and Leucovorin IV 5 Fluorouracil and Leucovorin IV	Drug: 5 Fluorouracil Arm B: 5 Fluorouracil 2000 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: 5 Fluorouracil 2400 mg/m2 IV every 2 weeks Other Name: 5-FU Drug: Leucovorin Arm B: Leucovorin 200 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: Leucovorin 400 mg/m2 IV every 2 weeks Other Name: Folinic Acid
Experimental: MM-398, 5-FU and Leucovorin MM-398 80 mg/m2, 5-FU and Leucovorin Q2W IV. Note: The published dose of ONIVYDE was expressed as the irinotecan hydrochloride trihydrate until October 2015. It is now expressed as the irinotecan free base. Converting a dose based on irinotecan hydrochloride trihydrate to a dose based on irinotecan free base is accomplished by substituting the Molecular Weight of irinotecan hydrochloride trihydrate (677.19 g/mole) with the Molecular Weight of irinotecan free base (586.68 g/mole), which results in a conversion factor of 0.866. 80 mg/m2 dose of irinotecan hydrochloride trihydrate is equivalent to 70 mg/ m2 of irinotecan free base.	Drug: MM-398 Arm A: MM-398 120 mg/m2 IV Q3W Arm C: MM-398 80mg/m2 IV Q2W Other Name: **PEP02** Drug: 5 Fluorouracil Arm B: 5 Fluorouracil 2000 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: 5 Fluorouracil 2400 mg/m2 IV every 2 weeks Other Name: 5-FU Drug: Leucovorin Arm B: Leucovorin 200 mg/m2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks Arm C: Leucovorin 400 mg/m2 IV every 2 weeks Other Name: Folinic Acid

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas

- Metastatic disease
- Documented disease progression after prior gemcitabine based therapy
- KPS >/= 70
- Adequate bone marrow function
- Adequate hepatic function
- Adequate renal function

Exclusion Criteria:

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- Clinically significant GI disorders
- Severe arterial thromboembolic events less than 6 months before inclusion
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
- Active infection or uncontrolled fever
- Pregnant or breast feeding patients

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01494506

Show 79 Study Locations

Sponsors and Collaborators

Merrimack Pharmaceuticals

Investigators

Study Director: Eliel Bayever, MD Merrimack Pharmaceuticals

More Information

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartsmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD, Chen LT; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016 Feb 6;387(10018):545-57. doi: 10.1016/S0140-6736(15)00986-1. Epub 2015 Nov 29. Erratum in: Lancet. 2016 Feb 6;387(10018):536.

Responsible Party:	Merrimack Pharmaceuticals
ClinicalTrials.gov Identifier:	NCT01494506 History of Changes
Other Study ID Numbers:	MM-398-07-03-01
Study First Received:	December 14, 2011
Results First Received:	November 25, 2015
Last Updated:	June 16, 2016
Health Authority:	United States: Food and Drug Administration

Keywords provided by Merrimack Pharmaceuticals:

Pancreatic cancer	Gemcitabine refractory pancreatic cancer
MM-398	Second line pancreatic cancer treatment
PEP02	Pancreatic cancer post gemcitabine therapy
Metastatic pancreatic cancer	

Additional relevant MeSH terms:

Pancreatic Neoplasms	Antimetabolites
Digestive System Neoplasms	Molecular Mechanisms of Pharmacological Action
Neoplasms by Site	Antineoplastic Agents
Neoplasms	Antiviral Agents
Endocrine Gland Neoplasms	Anti-Infective Agents
Digestive System Diseases	Enzyme Inhibitors
Pancreatic Diseases	Immunosuppressive Agents
Endocrine System Diseases	Immunologic Factors

Gemcitabine
Fluorouracil
Irinotecan
Antimetabolites, Antineoplastic

Physiological Effects of Drugs
Antineoplastic Agents, Phytogenic
Topoisomerase I Inhibitors
Topoisomerase Inhibitors

ClinicalTrials.gov processed this record on October 07, 2016