Electronic Acknowledgement Receipt

EFS ID:	42829222
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:	26-MAY-2021
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2021-05-26_01208-0007-01US_IDS_Transmittal_as_filed.pdf	121119 5753849232108c2d01bf4347ce858103923 73f67	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2021-05-26_01208-0007-01US_SB08_as_filed.pdf	1056118 d6e98645bc483c6f781c721dd91d05ca859a63b5	no	6
Warnings:					
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3	Non Patent Literature	Bouche_2004.pdf	604735 31db3150bede30a4aeb866155eefc701d72c1a8d	no	10
Warnings:					
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4	Non Patent Literature	Chiang_2016.pdf	429199 a0a29619c67ddb6290855f188142b58272bd9345	no	8
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	EP3337478_Comm_Notice_Sandoz_Opp.pdf	219402 c2250e5e0760daa1c17b9d78df194055ccebd069	no	5
Warnings:					
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6	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_Statement.pdf	2064113 4c7c47235df8e13e4cb8e6f6fb4ea2a91ddd06c1	no	22
Warnings:					
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7	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D1_NCT02551991.pdf	234689 bdeaa5651a3702455cbe4b180139bf00c843a352	no	4
Warnings:					
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8	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D2_VonHoff_2014_abstract.pdf	70107 2f1945d709903ed1143765bd29c3a076cfb5ec79	no	1
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9	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D3_Marsh_2015.pdf	1206345 ccff96dc8ddb505872116867e0c047ffd102bc8f	no	11
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10	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D4_Onivyde_PI_2015.pdf	1379308 9c3132be0766c9e3f46046be8731711b06e41908	no	18
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11	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D5_Carnevale_2016.pdf	1474432 3b719886f950bc3a93a7351c09e414506082b5a0	no	12
Warnings:					
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12	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D6_Dean_ASCO_2016_abstract.pdf	359476 76afe824d80a124453404cb746569a94468583d	no	5
Warnings:					
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13	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D7_Zhang_2016.pdf	804188 7e0f169b20950395191bd9b43b0b71c12f32d20a	no	7
Warnings:					
Information:					
14	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D8_Gaddy_AACR_2016_abstract.pdf	222953 0c7f7391a20ca8cfb15726a95113ca98d501305d	no	4
Warnings:					
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15	Other Reference-Patent/App/Search documents	EP3337478_Sandoz_Opp_D9_Parhi_2012.pdf	1437295 671a893d8ce195cd8b1c7da1b9a54d3c8ae1f1e6	no	9
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16	Other Reference-Patent/App/Search documents	EP3337478_Comm_Notice_GenericsUK_Opp.pdf	237663 59ea657c4d05b186ab5fbc68d4602ab299fab8b1	no	5
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17	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_Statement.pdf	751465 0c0c01cc0bc31273cfc53b1cd5444c373feb09b5	no	9
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18	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D10_Conroy_2011.pdf	1847843 4459b508d8b885a5d1a42e077c4ba73842c1cd37	no	9
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19	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D11_Gourgou-Bourgade_2013.pdf	1982716 a65238704ce5dce0e221367b7c92431173af4546	no	7
Warnings:					
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20	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D12_Ko_2013.pdf	1745627 cec3bf0b335de5d79504f86e404088f0af4b60f5	no	6
Warnings:					
Information:					
21	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D13_Hann_AACR_2007.pdf	316317 ba07a80f843cebff32d4f06f8de9840be26368c8	no	4
Warnings:					
Information:					
22	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D14_Chang_2015.pdf	1454903 a4a2421ee8ff2ca20e6b622accdd7d6ca99a35c5	no	8
Warnings:					
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23	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D15_Chen_2010_abstract.pdf	512872 8619c2fae2dc10401776fd4c54b1e0c964526e87	no	4
Warnings:					
Information:					
24	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D16_Mahaseth_2013_Pubmed_abstract.pdf	158589 f9177f0b9f139c5e4934f30b2d972b70615841ad	no	2
Warnings:					
Information:					
25	Other Reference-Patent/App/Search documents	EP3337478_GenericsUK_Opp_D17_Drummond_2006.pdf	1847765 f73ce2dab7e5a55eb1788f9815403805334 07379	no	8
Warnings:					
Information:					
26	Non Patent Literature	Koizumi_2005.pdf	113816 20550f4f6ea78f126207eace188f562d03e96fd6	no	6
Warnings:					
Information:					
27	Non Patent Literature	LoRusso_2011.pdf	1346974 eae786b8b31aa26612878bd965324bfe78642255	no	3
Warnings:					
Information:					
28	Non Patent Literature	Morise_2014.pdf	212295 2959b7b9ef2b8f2c09a98bc80931a3f8cf9250a1	no	6
Warnings:					
Information:					
29	Non Patent Literature	Wainberg_2021.pdf	259920 3241b00c35255c1819fa5513940cf508f385bd04	no	11
Warnings:					
Information:					
		Total Files Size (in bytes):	24472244		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Inventors:	
	Group Art Unit: 1612
Eliel BAYEVER et al.	
	Examiner: Gollamudi S. KISHORE
Application No.: 15/809,815	
Filed: November 10, 2017	
	Confirmation No.: 5137
Title: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

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 IDS Form PTO/SB/08. This Information Disclosure Statement is being filed after the filing of a Request for Continued Examination on February 25, 2021 and to the undersigned's knowledge before the mailing of an Office Action on the merits.

Copies of the listed non-US patent publication documents are enclosed.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they have been considered by making appropriate notations on the enclosed 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 the listed documents are material or constitute "prior art." If the Examiner applies a cited document against any claim of the application and Applicant determines that the cited document does not constitute "prior art," Applicant reserves the right to present to the Office the relevant facts and law regarding the appropriate status of the document.

Applicant further reserves the right to take appropriate action to establish the patentability of the claimed invention over the cited documents, should the Examiner apply one or more of the documents against any of the claims of the present application.

Please charge any fee required for entry of this Information Disclosure Statement, or credit any overpayment, to Deposit Account No. 506488.

Respectfully submitted,

McNeill Baur PLLC

Dated: May 26, 2021

By: /Mary R. Henninger/
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UNITED STATES PATENT AND TRADEMARK OFFICE

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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 08/26/2021

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/26/2021	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 GOLLAMUDI S KISHORE	Art Unit 1612	AIA (FITF) 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 02-25-2021.

☐ 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 21-23 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 21-23 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 ACTION

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.

The RCE dated 2-25-2021is acknowledged.

Claims included in the prosecution are 1, 4-15, 18-19 and 21-23.

1. 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 Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi).

Bayever et al discloses 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 discloses 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 does not disclose oxaliplatin, as recited in claim 9.

Conroy discloses FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy discloses 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 does not disclose that the irinotecan was liposomal irinotecan.

Since Bayever discloses 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 include 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 claims 1 and 19 limitation of 60 mg/m^2 oxaliplatin, the combination of Bayever (e.g., Bayever taught 85 mg/m^2 oxaliplatin at the abstract), though not silent the claimed amount of oxaliplatin, does not specifically teach 60 mg/m^2 oxaliplatin.

However, Melis teaches [abstract] that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients.

As such, oxaliplatin, and its amount, is recognized to have different effects (treatment of advanced pancreatic adenocarcinoma) 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 optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis.

The combination of Bayever, Conroy and Melis 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). 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.

Response to Arguments

Applicant's arguments filed 02-25-2021 have been fully considered but they are not persuasive.

Applicant argues that Bayever discloses treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2) in combination with 5-fluorocila (e.g., 2400 mg/m^2) and leucovorin (e.g., 400 mgm2 (l and d form) to a patient once every two weeks and Conroy describes administering a combination of 180 mg/m^2 of non-liposomal irinotecan, 85 mg/m^2 oxaliplatin, 5-FU and LV once every two weeks. According to applicant Melis is an abstract summarizing a phase I/II chemo-radiation study of continuous infusion of 200 mg/m^2 5-fluorouracil and escalating doses of oxaliplatin weekly for 5 weeks with concurrent radiation in patients with regionally advanced pancreatic cancer. Thus, according to applicant, Bayever, Conroy and Melis disclose treatment of pancreatic cancer with a different combination of therapeutic agents in different doses from that of the claimed invention.

These arguments are not persuasive since the rejection is made with combination of references using drugs which are routinely used in treating pancreatic cancer and the examiner sees no unexpected and surprising results using the art known pancreatic cancer treatment agents. With regard to the doses, if different, are routinely manipulatable parameters practiced by an artisan to obtain the best possible results. The Examiner also includes the previous responses by the previous Examiner in this regard.

With regard to applicant's arguments pertaining to Melis, as pointed out in the previous action, Melis was relied upon to show that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation (discussed above). Furthermore, cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); & MPEP 2145(IV)].

In response to Applicant's argument once again that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

2. Claims 4, 9, 18 and 23 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 Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) 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 Melis, has been discussed above.

Additionally, Bayever discloses 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 discloses 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, 18 and 23; liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming discloses 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 discloses 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 have been fully considered but they are not persuasive. The Examiner has already addressed Bayever et al (WO 2013/188586), Conroy et al (NEJM, 34(19), 2011, 1817) and Melis et al

Fleming is combined for its teaching of sequence of administration of drugs in general.

3. 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 Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) 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 Melis, has been discussed above.

Although, Bayever (2013) discloses 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 discloses 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 discloses 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 have been fully considered but they are not persuasive. The Examiner has already addressed Bayever et al (WO 2013/188586), Conroy et al (NEJM, 34(19), 2011, 1817) and Melis et al. Bayever (WO 2016/094402) is combined for the teachings of MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE. Applicant provides no specific arguments.

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).

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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.

4. Claims 1, 4-15, 18-19 and 21-23 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 Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi)

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 oxaliplatin. 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).

Melis taught [abstract] that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients.

Thus, it would have been prima facie obvious to use 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*. It would have been prima facie obvious to use oxaliplatin at 60 mg/m^2 because the said dosage is well tolerated in advanced pancreatic adenocarcinoma patients.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

The Applicants reiterated the above arguments regarding a failing to show a prima facie case of obviousness, to which the Examiner disagrees. A prima facie case of obviousness to combine each of the prior art was previously discussed.

5. Claims 1, 4-15, 18-19 and 21-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 10,980,795. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in both said patent and instant claims are drawn to treating metastatic adenocarcinoma of the pancreas using the same composition. Instant claims express the concentration of irinotecan in terms of free base and thus, claims in said patent and instant claims are obvious variants..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on Monday through Friday 6:30 AM - 4:00 PM.

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/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	GOLLAMUDI S KISHORE	1612

CPC - Searched*		
Symbol	Date	Examiner
(A61K31/519 or A61K9/1271 or A61K9/0019 or A61K31/475 or A61K31/436 or A61K47/20 or A61K31/282 or A61K31/4745 or A61K31/513 or A61K9/127 or A61K2300/00 or A61P43/00 or A61P35/04).cpc.	07/07/2021	GSK

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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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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	12	U.S. Patent Application No. 15/896,389: 2020-01-31 Final Office Action, 28 pages.
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	20	U.S. Patent Application No. 16/510,394: 2020-03-06 Non-Final Office Action, 15 pages.
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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-03-12
Name/Print	Mary R. Henninger	Registration Number	56992

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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	Art Unit	1612
	Examiner Name	Gollamudi S KISHORE
	Attorney Docket Number	01208-0007-01US

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	49	HUBNER R, et al., "Time Course of Selected Treatment-Emergent Adverse Events in NAPOLI-1: A Phase 3 Study of Liposomal Irinotecan (nal-IRI; MM-398) ± 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy." Poster presented at the European Society for Medical Oncology (ESMO) Annual Congress, Copenhagen, Denmark, October 7-11, 2016, 8 pages.
	50	HUBNER R, et al., Abstract 242P. "Effects of nal-IRI (MM-398) ± 5-Fluorouracil on Quality of Life (QoL) of Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine Based Therapy: Results From NAPOLI-1 ," Ann Oncol. 27(Supp_9):ix76 doi:10.1093/annonc/mdw582 (2016).

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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

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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The fee set forth in 37 CFR 1.17 (p) has been 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)	2021-02-25
Name/Print	Mary R. Henninger	Registration Number	56992

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Inventor Name Search Result

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Last Name = BAYEVER
First Name = ELIEL

Application#	Patent#	PG Pub#	Status	Date Filed	Title	Examiner Name	Inventor Name
09097397	Not Issued		161	06/16/1998	COMBINATION OF AN ANTISENSE OLIGONUCLEOTIDE AND AN OXYGEN RADICAL UP-REGULATOR FOR SELECTIVELY KILLING CANCER CELLS	LARSON,THOMAS	BAYEVER, ELIEL
09102607	Not Issued		161	06/23/1998	METHODS OF USE OF OLIGONUCLEOTIDES AND A SOURCE OF OXYGYN/HYDROYL OR NITROGEN RADICALS IN THE TREATMENT OF HYPERPROLIFERATIVE CELL DISEASE	SCHULTZ,JAMES	BAYEVER, ELIEL
11075269	Not Issued	20050272758	161	03/09/2005	Antineoplastic combinations of CCI-779 and rituximab	ANDERSON,JAMES	BAYEVER, ELIEL
14406776	9452162	20150182521	150	12/10/2014	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
14812950	9339497	20150328156	150	07/29/2015	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
14844500	9364473	20150374682	150	09/03/2015	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
14851111	9492443	20160074382	150	09/11/2015	Methods for Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan	STRONG,TORI	BAYEVER, ELIEL
14964571	Not Issued	20160346272	161	12/09/2015	TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN	BAEK,BONG-SOOK	BAYEVER, ELIEL
15059640	Not Issued	20160228428	161	03/03/2016	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
15241106	Not Issued	20170049775	161	08/19/2016	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	RONEY,CELESTE	BAYEVER, ELIEL
15241128	9717724	20160375004	150	08/19/2016	Methods for Treating Pancreatic Cancer Using Combination Therapies	STRONG,TORI	BAYEVER, ELIEL
15341377	Not Issued	20170065578	161	11/02/2016	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
15341619	Not Issued	20170049768	168	11/02/2016	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES	STRONG,TORI	BAYEVER, ELIEL
15378039	Not Issued	20170151226	161	12/09/2016	Treatment of Breast Cancer with Liposomal Irinotecan	BAEK,BONG-SOOK	BAYEVER, ELIEL
15403441	Not Issued	20170202840	161	01/11/2017	TREATMENT OF PANCREATIC CANCER WITH LIPOSOMAL IRINOTECAN	PACKARD,BENJAMIN	BAYEVER, ELIEL
15622513	Not Issued	20170368056	161	07/18/2017	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	STRONG,TORI	BAYEVER, ELIEL
15664230	Not Issued	20180008591	161	07/31/2017	Methods for Treating Pancreatic Cancer Using Combination Therapies	STRONG,TORI	BAYEVER, ELIEL
15809815	Not	20180078556	30	11/10/2017	Methods for Treating Metastatic	KISHORE,GOLLAMUDI	BAYEVER, ELIEL

	Issued				Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin		
15928649	Not Issued		160	03/22/2018	Treatment of Breast Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL
16012351	10286795	20190117643	150	06/19/2018	Methods For Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan	STRONG,TORI	BAYEVER, ELIEL
16012372	Not Issued	20190117644	140	06/19/2018	Methods For Treating Pancreatic Cancer Using Combination Therapies	REESE,HEIDI	BAYEVER, ELIEL
16036885	Not Issued	20190142822	161	07/16/2018	Treatment of Breast Cancer with Liposomal Irinotecan	BAEK,BONG-SOOK	BAYEVER, ELIEL
16711072	Not Issued	20200360367	30	12/11/2019	Treatment of Breast Cancer with Liposomal Irinotecan	BAEK,BONG-SOOK	BAYEVER, ELIEL
16805304	Not Issued		160	02/28/2020	Treatment of Breast Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL
16920830	Not Issued		160	07/06/2020	Methods For Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan	,	BAYEVER, ELIEL
17204278	Not Issued		19	03/17/2021	Methods For Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan	,	BAYEVER, ELIEL
60552122	Not Issued		159	03/11/2004	Antineoplastic combinations	,	BAYEVER, ELIEL
61784382	Not Issued		159	03/14/2013	METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62089685	Not Issued		159	12/09/2014	Treatment of Breast Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL
62207435	Not Issued		159	08/20/2015	Treatment of Pancreatic Adenocarcinoma with Liposomal Irinotecan	,	BAYEVER, ELIEL
62208269	Not Issued		159	08/21/2015	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	,	BAYEVER, ELIEL
62216736	Not Issued		159	09/10/2015	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	,	BAYEVER, ELIEL
62242796	Not Issued		159	10/16/2015	TREATMENT OF PANCREATIC ADENOCARCINOMA WITH LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62243935	Not Issued		159	10/20/2015	Treatment of Pancreatic Adenocarcinoma with Liposomal Irinotecan	,	BAYEVER, ELIEL
62244926	Not Issued		159	10/22/2015	Treatment of Pancreatic Adenocarcinoma with Liposomal Irinotecan	,	BAYEVER, ELIEL
62265469	Not Issued		159	12/09/2015	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND	,	BAYEVER, ELIEL
62272244	Not Issued		159	12/30/2015	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	,	BAYEVER, ELIEL
62278751	Not Issued		159	01/14/2016	TREATMENT OF PANCREATIC CANCER WITH LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62281458	Not Issued		159	01/21/2016	TREATMENT OF PANCREATIC CANCER WITH LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62281473	Not Issued		159	01/21/2016	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	,	BAYEVER, ELIEL
62302341	Not Issued		159	03/02/2016	METHODS FOR TREATING METASTATIC PANCREATIC	,	BAYEVER, ELIEL

					CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN		
62323245	Not Issued		159	04/15/2016	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	,	BAYEVER, ELIEL
62328839	Not Issued		159	04/28/2016	TREATMENT OF PANCREATIC CANCER WITH LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62341223	Not Issued		159	05/25/2016	TREATMENT OF PANCREATIC CANCER WITH LIPOSOMAL IRINOTECAN	,	BAYEVER, ELIEL
62343313	Not Issued		159	05/31/2016	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	,	BAYEVER, ELIEL
62351193	Not Issued		159	06/16/2016	Treatment of Triple Negative Breast Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL
62356649	Not Issued		159	06/28/2016	Treatment of Pancreatic Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL
62436479	Not Issued		159	12/06/2016	Treatment of Breast Cancer with Liposomal Irinotecan	,	BAYEVER, ELIEL

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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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	Attorney Docket Number	01208-0007-01US

	1	HUBNER R, et al., Abstract 3832. "Time Course of Selected Treatment Emergent Adverse Events (TEAES) in NAPOLI-1: A Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Cancer (mPAC) Previously Treated With Gemcitabine-Based Therapy," Ann Oncol. 27(6):207-242 10.1093/annonc/mdw371 (2016), 4 printed pages.
	2	HUBNER R, et al., Abstract 741P. "Prognostic Value of Baseline Neutrophil-to-Lymphocyte Ratio (NLR) for Predicting Clinical Outcome in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Patients Treated With Liposomal Irinotecan (nal-IRI) + 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV Alone," Ann Oncol. 28(Suppl_5):253 doi:10.1093/annonc/mdx369 (2017).
	3	HUBNER R, et al., Abstract O-004. "Effects of nal-IRI (MM-398) ± 5-fluorouracil on Quality of Life (QoL) in NAPOLI-1: A Phase 3 Study in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated with Gemcitabine." Annals of Oncology. 27(Suppl 2):ii118-ii128 (2016), 1 page.
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	5	HWANG J, et al., Abstract 4618. "A Randomized Phase II Study of FOLFOX or FOLFIRI.3 as Second-Line Therapy in Patients With Advanced Pancreatic Cancer Previously Treated With Gemcitabine-Based Chemotherapy," J Clin Oncol. 27(15_Suppl):4618 (2009), 2 printed pages.
	6	HWANG J, et. al., "Improving the Toxicity of Irinotecan/5-FU/Leucovorin: A 21-Day Schedule," Oncology. 17(9):37-43 (2003). Available at cancernetwork.com/view/improving-toxicity-irinotecan5-fu-leucovorin-21-day-schedule, 13 printed pages.
	7	IGNATIUS R, et al., "Presentation of Proteins Encapsulated in Sterically Stabilized Liposomes by Dendritic Cells Initiates CD8+ T-cell Responses in Vivo," Blood. 96(10):3505-13 (2000).
	8	ILSON D, "Nanolipoosomal Irinotecan Effective for Pancreatic Cancer," NEJM journal Watch, available at jwatch.org/na39795/2015/12/08/nanoliposomal-irinotecan-effective-pancreatic-cancer, (2015), 7 printed pages.
	9	IOKA T, et al., "Liposomal Irinotecan (nal-IRI) Plus 5-Fluorouracil/Levoleucovorin (5-FU/LV) vs 5-FU/LV in Japanese Patients (pts) With Gemcitabine-Refractory Metastatic Pancreatic Cancer (mPAC)." Poster presented at the European Society for Medical Oncology (ESMO) Asia 2019 Congress, Singapore, November 22-24, 2019, 9 pages.
	10	IOKA T, et al., Abstract 132P. "Liposomal Irinotecan (nal-IRI) Plus 5-Fluorouracil/Levoleucovorin (5-FU/LV) vs 5-FU/LV in Japanese Patients (pts) With Gemcitabine-Refractory Metastatic Pancreatic Cancer (mPAC)," Ann Oncol. 30 (Suppl_9):ix47-ix48 doi:10.1093/annonc/mdz422 (2019).
	11	IOKA T, et al., Abstract 274TiP. "A Randomized Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI, BAX2398)-Containing Regimen in Japanese Patients With Metastatic Pancreatic Adenocarcinoma (mPAC)," Ann Oncol. 27 (Supp_9):ix84-ix85 doi:10.1093/annonc/mdw582 (2016).

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	12	JAMESON G, et al., "Adverse Events in Patients with Metastatic Pancreatic Cancer Receiving Liposomal Irinotecan: Understanding the Occurrence and How Management Affects Patient Outcomes." Poster presented at the Oncology Nursing Society (ONS) Annual Conference, Washington, DC, May 17-20, 2018, 7 pages.
	13	JAMESON G, et al., Abstract 1. "Adverse Events in Patients with Metastatic Pancreatic Cancer Receiving Liposomal Irinotecan: Understanding the Occurrence and How Management Affects Patient Outcomes," Oncology Nursing Society (ONS) 43rd Annual Congress, available at ons.confex.com/ons/2018/meetingapp.cgi/Paper/2970, (2018), 2 pages.
	14	KANG S and SAIF M, "Optimal Second Line Treatment Options for Gemcitabine Refractory Advanced Pancreatic Cancer Patients. Can We Establish Standard of Care with Available Data?," JOP. J Pancreas (Online) 9(2):83-90 (2008).
	15	KATOPODIS O, et. al., "Second-Line Chemotherapy With Capecitabine (Xeloda) and Docetaxel (Taxotere) in Previously Treated, Unresectable Adenocarcinoma of Pancreas: The Final Results of a Phase II Trial," Cancer Chemother Pharmacol. 67(2):361-8 (2011). Epub 2010.
	16	KIM G, et al., "Clinical Pathway Implications and Real-World Characteristics and Outcomes for Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With First Line Category 1 National Comprehensive Cancer Network (NCCN) Regimens." Poster presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020, September 19-21, 2020, 6 pages.
	17	KIM G, et al., "Impact of Treatment Sequence on Overall Survival in Metastatic Pancreatic Cancer Patients Treated with Liposomal Irinotecan in the Real-World Setting." Poster presented at the Hematology Oncology Pharmacy Association (HOPA) Annual Conference, Tampa, FL, March 11-14, 2020, 7 pages.
	18	KIM G, et al., Abstract 1564P. "Clinical Pathway Implications and Real-World Characteristics and Outcomes for Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With First Line Category 1 National Comprehensive Cancer Network (NCCN) Regimens," Ann Oncol. 31(Suppl_4):S881-S897 10.1016/annonc/annonc285 (2020), 2 printed pages.
	19	KIM G, et al., Abstract e16740. "Real-World Use of Liposomal Irinotecan-Based Regimens Among Patients (pts) With Metastatic Pancreatic Adenocarcinoma (mPDAC) in the United States (U.S.)," J Clin Oncol. 38(15_Suppl):e16740 DOI: 10.1200/JCO.2020.38.15_suppl.e16740 (2020), 2 printed pages.
	20	KIM H, et. al., "Phase II Study of Palliative S-1 in Combination With Cisplatin as Second-Line Chemotherapy for Gemcitabine-Refractory Pancreatic Cancer Patients," Oncol Lett. 3(6):1314-8 (2012).
	21	KIM Y, et. al., "Phase II Study of 5-Fluorouracil and Paclitaxel in Patients With Gemcitabine-Refractory Pancreatic Cancer," Cancer Chemother Pharmacol. 63(3):529-33 (2009). Epub 2008.
	22	KINDLER H, et. al., "Arsenic Trioxide in Patients With Adenocarcinoma of the Pancreas Refractory to Gemcitabine: A Phase II Trial of the University of Chicago Phase II Consortium," Am J Clin Oncol. 31(6):553-6 (2008).

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	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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Name/Print	Mary R. Henninger	Registration Number	56992

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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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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-03-12
Name/Print	Mary R. Henninger	Registration Number	56992

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Filed 2016-08-19 • Published 2019-10-03

Combination comprising for use in the treatment of metastatic pancreatic cancer in human patients not treated previously received by metastatic pancreatic cancer chemotherapy, liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil a is an anti-tumor therapy is characterized Rukoto ...

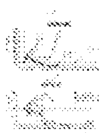
Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapy ...

WO EP US CN JP KR AU BR CA ES HK IL MX PT RU SG SI TW · KR20180039087A · 사라 에프 블랑쳇 · 입센 바이오팜 리미티드

Priority 2015-08-21 • Filed 2016-08-19 • Published 2018-04-17

Combination therapy regimens involving liposomal irinotecan, oxaliplatin and 5-fluorouracil are useful in the treatment of pancreatic cancer, including treatment of patients diagnosed with metastatic adenocarcinoma of the pancreas not previously treated. Combination therapy may include ...

Gastric cancer treatment using combination therapy including liposomal ...

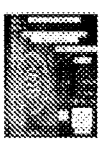


WO EP US CN JP KR AU BR CA EA IL MX PH RU SG TW · KR20190077441A · 빈 장 · 입센 바이오팜 리미티드

Priority 2016-11-02 • Filed 2017-11-01 • Published 2019-07-03

Combination therapy regimens comprising liposomal irinotecan, oxaliplatin and 5-fluorouracil are useful in the treatment of gastric cancer, including the treatment of patients diagnosed with previously untreated gastric cancer. This combination regimen may include administration of liposomal ...

Cancer tretments

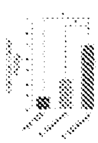


WO EP US CN JP KR AU BR CA EA GR MA MX NO RS TN ZA · KR20090023548A · 파스이니오스 푸리카스 · 파스이니오스 푸리카스

Priority 2006-03-03 • Filed 2007-03-05 • Published 2009-03-05

The present invention relates to liposome comprising encapsulated oxaliplatin and methods for making encapsulated oxaliplatin. The invention also relates to liposomes comprising oxaliplatin and another anticancer drug. The liposome sof the invention are useful in cancer treatments.

Mesoporous silica nanoparticles with a lipid bilayer coating for cargo delivery



WO EP US CN JP KR AU CA · US10765636B2 · Andre E. Nel · The Regents Of The University Of California

Priority 2016-01-08 • Filed 2018-10-18 • Granted 2020-09-08 • Published 2020-09-08

CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation of U.S. Ser. No. 15/798,287, filed Oct. 30, 2017, which is a continuation of International Application PCT/US2017/012625, with an international filing date of Jan. 6, 2017, which claims benefit of and priority to U.S. Ser.

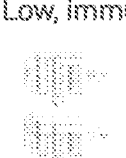
RNA interference compositions targeting heat shock protein 90 and methods of ...

WO US · US10006030B2 · Amotz Shemi · Silenseed Ltd.

Priority 2014-07-14 • Filed 2015-07-14 • Granted 2018-06-26 • Published 2018-06-26

This disclosure relates to RNA interference (RNAi) compositions that target expression of heat shock protein 90 (HSP90) in a subject. Polymeric delivery devices for providing the RNAi compositions are also described, as are methods of treating cancer using the described RNAi compositions.

Low, immune enhancing, dose MTOR inhibitors and uses thereof



WO EP US CN JP KR AU BR CA EA MX TW · US10286069B2 · Joan Mannick · Novartis Ag

Priority 2013-11-13 • Filed 2018-06-25 • Granted 2019-05-14 • Published 2019-05-14

The present invention relates, in part, to compositions and methods for enhancement of an immune response by partial mTOR inhibition, e.g., with low, immune enhancing, doses of an mTOR inhibitor, such as RAD001.

Methods of using MEK inhibitors

WO EP US CN JP AU CA ES HK PL TR · AU2007334402B2 · Peter Lamb · Exelixis, Inc.

Priority 2006-12-14 • Filed 2007-12-14 • Granted 2014-02-13 • Published 2014-02-13
The present invention provides methods of treating cancer by administering a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments.

IGFBP2 inhibitor

WO EP US JP AT CA ES • JP5815167B2 • マンク・メルク・シャープ・アンド・ドーム・コーポレーションMerck Sharp & Dohme Corp.
Priority 2006-06-30 • Filed 2012-09-10 • Granted 2015-11-18 • Published 2015-11-18
A kit for monitoring the effect of an IGF1R inhibitor on an IGF1R receptor in a subject administered with an IGF1R inhibitor, comprising: The kit includes means for measuring IGFBP2 levels in the subject's body and instructions for assessing IGFBP2 levels in the subject's body over an extended ...

Treatment of cancer using TLR3 agonists

WO EP US AU BR CA EA MX • US8409813B2 • Fabrice Andre • Institut Gustave Roussy
Priority 2004-11-19 • Filed 2010-05-26 • Granted 2013-04-02 • Published 2013-04-02
The present invention relates generally to the fields of genetics and medicine. More specifically, the present invention relates to improved methods of treating cancers using a TLR3 agonist, by assessing the expression of a TLR3 receptor by cancer cells.

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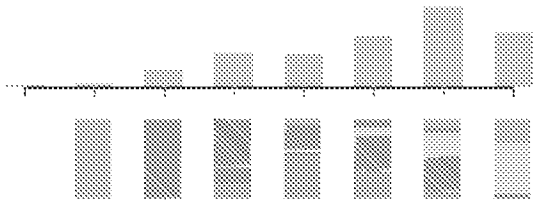

Relative count of top 5 values

Assignees	Inventors	CPCs
Vertex Pharmaceuticals Incorporated		2.4%
Genentech, Inc.		2.1%
H. Lee Moffitt Cancer Center And Research Institute, Inc.		1.8%
University Of Southern California		1.4%
Celgene Corporation		1.1%

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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	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	1	WANG-GILLAM A, et al., Abstract 459. "Nomogram for Predicting Overall Survival (OS) in Patients (pts) Treated With Liposomal Irinotecan (nal-IRI) ± 5-Fluorouracil/Leucovorin (5-FU/LV) in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy in NAPOLI-1," J Clin Oncol. 36(4_Suppl):459 DOI: 10.1200/JCO.2018.36.4_suppl.459 (2018), 2 printed pages.
	2	WANG-GILLAM A, et al., Abstract e15795. "The Prognostic Value of Baseline Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) for Predicting Clinical Outcome in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan (nalIRI; MM398) + 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV," J Clin Oncol. 35(15_Suppl):e15795 DOI: 10.1200/JCO.2017.35.15_suppl.e15795 (2017), 3 printed pages.
	3	WANG-GILLAM A, et al., Abstract e16204. "A Survival Prediction Nomogram for Liposomal Irinotecan (nal-IRI)+5-Fluorouracil/Leucovorin (5-FU/LV) in Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy," J Clin Oncol. 36(15_Suppl):e16204 DOI: 10.1200/JCO.2018.36.15_suppl.e16204 (2018), 2 printed pages.
	4	WANG-GILLAM A, et. al., letter to editor, "Nanoliposomal Irinotecan in the Clinical Practice Guideline for Metastatic Pancreatic Cancer: Applicability to Clinical Situations," J Clin Oncol. 35(6):689-90 (2017). Epub 2016.
	5	XIONG H, et. al., "Phase 2 Trial of Oxaliplatin Plus Capecitabine (XELOX) as Second-line Therapy for Patients With Advanced Pancreatic Cancer," Cancer. 113(8):2046-52 (2008).
	6	YU K, et al., "Hospitalizations and Real-World Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review," Poster presented at the Academy of Managed Care Pharmacy, Nexus (AMCP, Nexus): virtual meeting, week of October 19, 2020, 9 pages.
	7	YU K, et al., Abstract C3. "Hospitalizations and Real-World Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review," J Manag Care Spec Pharm. 26(10-a):S19 (2020).
	8	YU K, et al., "A US Multicenter Chart Review Study of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy." Poster presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) All Access, September 16-17, 2020, 8 pages.
	9	YU K, et al., "Real-World Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review." Poster presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020, September 19-21, 2020, 9 pages.
	10	YU K, et al., Abstract 1555P. "Real-World Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review," Ann Oncol. 31(Suppl_4):S950-S951 doi.org/10.1016/j.annonc.2020.08.2038 (2020), 2 printed pages.
	11	YU K, et al., Abstract e16733. "A Multicenter Chart Review Study of Patients with Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy," J Clin Oncol. 38(15_Suppl): e16733 DOI: 10.1200/JCO.2020.38.15_suppl.e16733 (2020), 4 printed pages.

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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	12	YU K, et al., Abstract PO-3727. "A US Multicenter Chart Review Study of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy," International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), September 14, 2020, available at eventscribe.com/2020/ICPEAllAccess/PosterTitles.asp?pfp=PosterTitles, 1 page.
	13	YU X, et. al., "Targeted Drug Delivery in Pancreatic Cancer," Biochim Biophys Acta. 21805(1):97-104 (2010). Epub 2009, author manuscript version, 16 pages.

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EXAMINER SIGNATURE

Examiner Signature	/GOLLAMUDI S KISHORE/	Date Considered	07/07/2021

*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.

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	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

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)	2021-02-25
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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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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	1449	08/26/2021	263266-421428
	1449	08/26/2021	263266-421428
	1449	08/26/2021	263266-421428
	1449	08/26/2021	263266-421428
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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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In re Application of: Eliel BAYEVER et al.	Group Art Unit: 1612
Application No.: 15/809,815	Examiner: Gollamudi S. Kishore
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 Kishore:

Applicant responds to the Non-Final Office Action mailed August 26, 2021. The period for response has been extended to February 26, 2022, by request for extension of three months and payment of extension fees herewith. Please amend the above-identified application as follows:

LISTING OF THE CLAIMS:

The pending claims are listed below. No amendments are included.

1. (Previously Presented) 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 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 the (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. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over 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. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes 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).

12. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes 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).

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 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).

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. (Previously Presented) 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 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 the (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. (Previously Presented) The method of claim 1, 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. (Previously Presented) The method of claim 19, 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. (Previously Presented) 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.

REMARKS

I. Status of Claims

Claims 1, 4-15, 18-19, and 21-23 are pending in the application. Applicant includes a listing of the pending claims here for the Examiner's convenience. No amendments are made herein.

II. Rejections Under 35 U.S.C. § 103

Claims 1, 5-8, 10 and 19

The Examiner maintains the rejection of claims 1, 5-8, 10 and 19 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 Melis et al., The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) ("Melis"). Action at page 2. The Examiner alleges that "it would have been prima facie obvious to one of ordinary skill in the art to include 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.* at page 3. The Examiner also alleges that "result effective variables can be optimized by routine experimentation, and it would have been prima facie obvious to optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis." *Id.* at pages 2-3.

Applicant incorporates by reference the arguments presented in the January 7, 2020, Non-Final Office Action Response and February 25, 2021, Final Office Action Response. The combination of references fails to teach the specific antineoplastic therapy *consisting of* the claimed dosages of liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU for "treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent." As previously set forth, Bayever, Conroy, and Melis disclose treatment of pancreatic cancer with a *different* combination of therapeutic agents in *different* doses from that of the claimed invention. The Examiner acknowledges that the references teach different combinations of agents in different dosages, but nonetheless asserts that their teachings can be

combined. Applicant respectfully traverses for the reasons previously presented and described in detail below.

No motivation to combine the references

The Examiner acknowledges "Bayever does not disclose oxaliplatin," but maintains that Bayever discloses treatment of "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)" 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. *See* Action at page 2. The Examiner asserts that it would have been obvious to include oxaliplatin within the methods of Bayever based on the teachings of Conroy and Melis. *See* Action at page 3. The Examiner acknowledges that Conroy does *not* disclose liposomal irinotecan and does not specifically teach 60 mg/m^2 of oxaliplatin pursuant to the claims. Action at page 3.

Applicant respectfully submits that a person of ordinary skill in the art would *not* have modified the regimen in Conroy and/or combined the teachings of Conroy with Bayever (or Melis) to reach the claimed methods based on the teachings of the references when viewed as a whole. In contrast to the claims, Conroy discloses administering 180 mg/m^2 non-liposomal irinotecan, 85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin, and a higher dose of 2,800 mg/m^2 total 5-fluoruracil (400 mg/m^2 bolus of 5-fluorouracil before a 2,400 mg/m^2 administration).

Conroy	**Claim 1 regimen**
180 mg/m^2 non-liposomal irinotecan	**60 mg/m^2** liposomal irinotecan
85 mg/m^2 oxaliplatin	**60 mg/m^2** oxaliplatin
400 mg/m^2 LV	**400** mg/m^2 LV
2800 mg/m^2 5-FU	**2400** mg/m^2 5-FU

There is no mention of any liposomal irinotecan in Conroy or adjusting any of the dosages in Conroy towards those required by the claims. Conroy describes the FOLFIRINOX regimen that has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic pancreatic cancer since 2011. *See* the present Specification at page 2, lines 9-11. Despite acknowledging the existence of the FOLFIRINOX regimen as a combination chemotherapy regimen for pancreatic cancer, nowhere does Bayever teach or suggest incorporating oxaliplatin into its therapeutic regimen. *See* Bayever at 1.

Additionally, there is no basis for combining Conroy and Bayever because there is no basis for combining teachings regarding second-line therapy with teachings regarding first-line therapy. Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® (irinotecan liposome injection), which is indicated for the treatment of patients with metastatic adenocarcinoma of the pancreas *after* disease progression following gemcitabine-based therapy—i.e., as a *second-line therapy* for metastatic pancreatic cancer. *See* www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf and the present Specification at page 2, lines 19-22; *see* Response to Final Office Action filed February 25, 2021, at page 9. By contrast, Conroy describes assessing FOLFIRINOX "as compared with gemcitabine as first-line therapy." *See* Conroy at abstract. As set forth in more detail below, a person of ordinary skill in the art would not combine teachings regarding first-line cancer treatments and second-line cancer treatments.

The Examiner acknowledges that neither Bayever nor Conroy teach the claimed dosage of 60 mg/m^2 of oxaliplatin, and cites Melis for allegedly teaching that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients. *See* Action at page 3-4. The Examiner states, "Melis was relied upon to show that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation." Action at page 5. The teachings of Melis, however, fail to establish that the dosage of oxaliplatin in the claimed regimen would be a "result effective variable" in view of the knowledge of the art. The MPEP states that a "result effective variable" as used in an "obvious to try" line of reasoning is one which is known in the art to "achieve[] a recognized result." *See* MPEP at § 2144.05(II)(B)-(C). In other words, a "result effective variable" is one that can be varied to have a predictable effect on the final outcome. *See* MPEP at § 2143. Melis is a one-paragraph abstract summarizing a chemo-radiation study in regionally advanced pancreatic cancer patients using a combination therapy that does *not* contain irinotecan *or* leucovorin. Melis fails to recognize *any* predictable outcome that may be achieved by varying the dose of oxaliplatin when administered in combination with irinotecan and/or leucovorin, much less any predictable tolerability *or* efficacy when co-administered at any particular doses, in the claimed metastatic patient population. As the Examiner acknowledges, a person of ordinary skill in the art would have known the activity of oxaliplatin to be affected by co-administration of other drugs. *See* Action at page 3.

However, the cited references, including Melis, fail to address the effects of co-administration of the other drugs in the claimed regimen on the efficacy and tolerability of oxaliplatin. As such, the dosage of oxaliplatin cannot be considered a "result-effective variable" that would achieve a recognized result when administered in the claimed therapy.

Additionally, there is no basis for combining the teachings of Melis with Bayever and/or Conroy.[1] Melis assesses the administration of "continuous infusion 5FU (200 mg/m^2) and oxaliplatin weekly for 5 weeks" with "concurrent radiation in patients presenting with regionally advanced disease." *See* Melis at abstract. As set forth above, there is nothing in Melis suggesting its teachings can apply beyond the combination 5FU (200 mg/m^2) and oxaliplatin. *Id.* While Melis may teach that administering, "up to 60 mg/m^2 oxaliplatin" was "well tolerated" in a small number of patients, Melis *must be viewed as a whole*. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *See In re Wesslau*, 353 F.2d 238 (CCPA 1965); MPEP § 2141.02(VI). When viewed as a whole, Melis would *not* be combined with Bayever and/or Conroy to reach the claimed regimen. *See* Response to Final Office Action filed February 25, 2021, at page 7-8. As reiterated below, there is no motivation to combine the references or otherwise modify Melis to reach the claimed methods:

First, the Melis Study involved patients with locally advanced pancreatic cancer and thus necessarily ***excluded*** patients with metastatic disease; as such it would not be combined with Conroy and/or Bayever to achieve the claimed method. *See also* Amodeo et al, "Can we downstage locally advanced pancreatic cancer to resectable? A phase I/II study of induction oxaliplatin and 5-FU chemoradiation," J Gastrointest Oncol, 9(5):922-935, 2018 ("Amodeo") (cited in the January 7, 2020 IDS) at p. 924. Second, the Melis Study involved ***weekly*** administration of 60 mg/m^2 oxaliplatin in contrast to the "every two weeks" co-administration

[1] The Office Action at pages 5-6 cites *In re Keller*, 642 F.2d, 208 USPQ 871 (CCPA 1981) and seems to allege Applicant was "attacking references individually." However, "[w]here an applicant's reply establishes that each of the applied references fails to teach a limitation and addresses the combined teachings and/or suggestions of the applied prior art, the reply as a whole does not attack the references individually as the phrase is used in *Keller* and reliance on *Keller* would not be appropriate." *See* MPEP at § 2145.

schedule recited in the claims, Conroy, and Bayever (*see* claim 3). It would have been well known that adjusting the administration frequency of a dosage regimen could have implications on the efficacy and tolerability of the treatment. Third, not only does Melis fail to disclose any irinotecan and leucovorin (and therefore would not be combined with Conroy and/or Bayever on that basis), but even the method of dosing 5-fluorouracil and oxaliplatin differs from the other cited references and the claims, which could also have implications on the efficacy and tolerability of the treatment. The Melis Study included continuous infusion of 200 mg/m^2 5-fluorouracil daily and oxaliplatin weekly for 5 weeks in dose escalation cohorts, which differs from the claimed coadministration of 2,400 mg/m^2 5-fluorouracil once every two weeks and the 400 mg/m^2 bolus of 5-fluorouracil before a 2,400 mg/m^2 administration disclosed in Conroy. Fourth, there would have been no reason to combine the teachings of Melis with that of Bayever and/or Conroy because the Melis treatment regime did not result in improved outcomes compared to other combination therapies for locally advanced pancreatic cancer. *See* Amodeo at p. 933. Fifth, patients who remained unresectable for cure but did not progress continued on a modified FOLFOX6 regime involving a higher 85 mg/m^2 dose of oxaliplatin every two weeks. *See* Melis abstract and Amodeo at p. 924. If anything, the teachings of Melis would have *discouraged* treatments using 60 mg/m^2 of oxaliplatin once every two weeks.

No reasonable expectation of success

Even if there was motivation to combine the cited reference, there can be no *prima facie* case of obviousness as the combination of references fail to establish a reasonable expectation of success in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent. The rejection simply fails to account for the many factors, such as patient population, disease severity, drug combination, dose, dosing schedule, drug-drug interactions, and overlapping toxicities, that each affect tolerability and efficacy of a particular cancer treatment method.

Initially, in contrast to the assertions of the Examiner, there would have been no reasonable expectation that including oxaliplatin from a first-line treatment regimen (e.g., as disclosed in Conroy) into a second-line treatment regimen (e.g., as disclosed in Bayever) would yield an effective and tolerable first-line treatment pursuant to the claims. In general, results

from second-line treatments cannot establish a reasonable expectation of similar results in treating patients who have not previously received an antineoplastic agent (and vice versa). Expectations of efficacy and safety of treatments are entirely different at these two separate stages: in second-line therapy, the tumor may have become more malignant and difficult to treat; patients receiving second-line therapy are also likely significantly more sick and less able to tolerate therapy than those receiving a first-line therapy. As an example of the general unpredictability of moving from one line to another, Conroy teaches that when used as a first-line therapy, FOLFIRINOX yielded prolonged median overall survival compared to gemcitabine, whereas the same results were not observed when used as second-line therapy. *See, e.g.*, Conroy at 1821 (smaller cohort received second-line therapy).

If a person of ordinary skill in the art were to combine the teachings of Bayever and Conroy, the skilled person would only have been led to use the 85 mg/m^2 dose of oxaliplatin disclosed in Conroy's FOLFIRINOX regimen, which was found to be safe and effective. *See* Conroy at 1824. The Examiner, however, has not established that a person of ordinary skill in the art would have combined the 85 mg/m^2 oxaliplatin of Conroy with the 60 mg/m^2 liposomal irinotecan regimen of Bayever, with an expectation of success. Conroy does not provide any comparison of liposomal vs. non-liposomal irinotecan with oxaliplatin or provide any data on how reducing the overall dosage of 5-FU, oxaliplatin, or irinotecan would affect treatment. Bayever similarly does not provide any teachings regarding how adding oxaliplatin to its combination regimen may affect efficacy, tolerability, or even the PK parameters of the liposomal irinotecan. *Cf.* Bayever at page 20. In actuality, the combination of 85 mg/m^2 oxaliplatin with 60 mg/m^2 liposomal irinotecan, 5-FU, and LV was ***not tolerable*** as a first-line treatment in patients with metastatic pancreatic cancer. *See* Wainberg Cohort C (described below and in the Wainberg article at 17); *see also* Specification at Tables 2 and 17 (level -2B).

A skilled person, when provided the doses in Conroy that were found to be safe and effective, would not instead have chosen a *different* dose of oxaliplatin that had not been shown to be safe and efficacious in combination with irinotecan, leucovorin, and 5-FU. None of the cited references suggest lowering the dose of oxaliplatin of Conroy with any expectation that reducing the dose would yield a safe and effective treatment. Indeed, none of the references teach or suggest tolerability *and* efficacy of 60 mg/m^2 oxaliplatin in combination with the

claimed liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU dosages. The Examiner cites to Melis for teaching a 60 mg/m^2 oxaliplatin dose, but Melis does not remedy the deficiencies of Conroy or Bayever with respect to establishing an expectation of success using the claimed regimen. In actuality, combining the 60 mg/m^2 oxaliplatin dose cited by the Examiner in Melis with 80 mg/m^2 liposomal irinotecan, 5 FU, and LV was similarly ***not tolerable*** as a first-line treatment. *See* Wainberg Cohort A (described below and in the Wainberg article at 17); *see also* Specification at page 3, lines 23-26 and Example 4 (e.g., Table 15, page 62, lines 16-19, and page 64, lines 4-7).

Indeed, rather than pointing to specific teachings establishing a reasonable expectation of success of the alleged combination, the Examiner relies on asserting that the dosage of oxaliplatin is a "result effective variable" that can be optimized by routine experimentation and doses are "routinely manipulatable parameters practiced by an artisan to obtain the best possible results." *See* Action at pages 3 and 5. As set forth above, Melis does not provide motivation to combine with Bayever and/or Conroy and otherwise fails to establish that the dosage of oxaliplatin is a "result effective variable." Importantly, Melis fails to teach how different dosages of oxaliplatin when co-administered with irinotecan and/or leucovorin effects tolerability *and* efficacy—both of which must be assessed to determine the success of cancer treatment in the claimed metastatic patient population.

The Federal Circuit has indicated that "to have a reasonable expectation of success, one must be motivated to do more than merely to 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.'" *See Medichem v. Rolabo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). The Federal Circuit has also recently stated that only with the benefit of hindsight could a person of ordinary skill in the art have had a reasonable expectation of success in view of the asserted references in a case involving cancer treatment. *See OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375, 1378, 1381 (Fed. Cir. 2019) (stating that "[c]ancer treatment is highly unpredictable" and reversing the PTAB's finding of obviousness in a case involving non-small cell lung cancer treatments). The Conroy reference at page 1823 exemplifies the general difficulties in predicting efficacy and

tolerability of cancer treatments, describing the addition of known cytotoxic and targeted agents to gemcitabine treatment as having "almost invariably provided no significant survival improvement, despite an improvement in response rates in some trials." The Specification also suggests difficulties in successfully predicting the clinical effects of modifying known treatment regimens, indicating modified regimens often have "unknown effects on the efficacy and safety." *See* Specification at page 2, lines 15-16. Accordingly, without more, the cited references are simply insufficient to establish the requisite degree of predictability for obviousness. *See* MPEP § 2143.02.

Unexpected Results

Respectfully, the Examiner has not specifically commented on and thus has not seemed to consider the unexpected results that were previously presented. The Office Action states "the examiner sees no unexpected and surprising results using the art known pancreatic cancer treatment agents. With regard to the doses, if different, are routinely manipulatable parameters practiced by an artisan to obtain the best possible results." *See* Action at page 5. To the extent the Examiner did not consider the data presented, the MPEP indicates evidence of unexpected results *must* be considered when properly presented. *See* MPEP § 2145.

The technical results in the instant specification and described herein show that the combination regimens suggested by the Examiner based on the cited references are *not* tolerable, but that the claimed regimen are. Surprisingly, the claimed lower dose combinations and compositions of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 5-FU, and LV are tolerable and, despite the lower combined dose, achieved unexpected therapeutic effects over that of the standard first-line FOLFIRINOX regimen of Conroy. *See* Wainberg Cohort B (described below).

The 2020 Wainberg abstract, poster, presentation, and article (cited in the May 26, 2021 IDS)[2] report data resulting from the clinical protocol described in Example 3 of the instant

[2] Wainberg Z, et al., "First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study," Ann Oncol. 31(Suppl 3):S241 doi.org/10.1016/j.annonc.2020.04.076 (2020) ("Wainberg abstract"), and corresponding poster ("Wainberg poster") and presentation ("Wainberg (continued...)

application and builds on the trial results from Example 4 in the specification. 87.5% of patients receiving the claimed dosage regimen (Cohort B) had metastatic disease at diagnosis. *See* Wainberg article at page 17. Four cohorts of patients with unresectable, locally advanced or metastatic pancreatic ductal adenocarcinoma were treated on days 1 and 15 of each 28-day cycle with 5-FU 2400 mg/m^2 and LV 400 mg/m^2 in combination with the following doses of liposomal irinotecan and oxaliplatin[3]:

- Cohort A: 80 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("80/60");
- **Cohort B: 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("60/60");**
- Cohort C: 60 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin ("60/85"); and
- Cohort D: 65 mg/m^2 liposomal irinotecan and 70 mg/m^2 oxaliplatin ("65/70").

See Wainberg article at page 16. Each of the therapies of Cohorts A (80/60), C (60/85), and D (65/70) were not tolerable, whereas Cohort B (60/60)—which reads upon the claimed regimen—was tolerable. *See* Table 2 of the Wainberg poster and slide 8 of the Wainberg presentation; Wainberg article at page 17.

Wainberg Cohort A	Wainberg Cohort B (Claim 1)	Wainberg Cohort C	Wainberg Cohort D
70 mg/m^2 free base dose equivalent to 80 mg/m^2 liposomal irinotecan	50 mg/m^2 free base dose equivalent to **60 mg/m^2** liposomal irinotecan	50 mg/m^2 free base dose equivalent to 60 mg/m^2 liposomal irinotecan	55 mg/m^2 free base dose equivalent to 65 mg/m^2 liposomal irinotecan
60 mg/m^2 oxaliplatin	**60 mg/m^2** oxaliplatin	85 mg/m^2 oxaliplatin	70 mg/m^2 oxaliplatin
400 mg/m^2 LV	**400** mg/m^2 LV	400 mg/m^2 LV	400 mg/m^2 LV
2400 mg/m^2 5-FU	**2400** mg/m^2 5-FU	2400 mg/m^2 5-FU	2400 mg/m^2 5-FU

(…continued)
presentation") presented at the European Society for Medical Oncology (ESMO) World; and Wainberg et al., "First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study," European Journal of Cancer 151 at page 20 (2021) 14e24, https://doi.org/10.1016/j.ejca.2021.03.028 ("Wainberg article"). The Wainberg article was not discussed in the Response filed February 25, 2021.

[3] The 50, 55, and 70 mg/m^2 free base doses of liposomal irinotecan referenced in the Wainberg abstract, poster, and presentation are equivalent to 60, 65, and 80 mg/m^2 doses, respectively, of liposomal irinotecan based on the molecular weight of irinotecan hydrochloride trihydrate. *See* Specification at page 8, lines 12-19 and page 67, lines 10-14.

The cohort of patients treated with the only tolerable dose of oxaliplatin and liposomal irinotecan tested (60/60) unexpectedly resulted in primary efficacy outcomes ***higher*** than that of the currently preferred FOLFIRINOX regimen as reported in Conroy. Specifically, the median overall survival (OS) was 12.6 months, the median progression free survival (PFS) was 9.2 months, and the objective response rate (ORR) was 34.4 % for the 32 patients[4] from both the Cohort B and dose-expansion study. *See* Results section of the Wainberg abstract and poster and slides 9 and 10 of the Wainberg presentation; Wainberg article at page 21. These primary efficacy outcomes are each ***higher*** than those reported in Conroy for FOLFIRINOX (OS of 11.1 months, PFS of 6.4 months, and ORR of 31.6%). *See* Conroy at page 1817. An increase of nearly 3 months in progression free survival (with no overlap at all in the 95% confidence interval) is a significant efficacy improvement to the treatment of patients with pancreatic adenocarcinoma, with an increase in mean overall survival of 1.5 months. Additionally, where 9% of patients receiving FOLFIRINOX in the Conroy regimen experienced grade 3-4 sensory neuropathy—a "particular concern with oxaliplatin-containing regimens"—no cases were reported by the patients receiving the claimed regimen. *See* Wainberg article at 21 (indicating that for "persistent grade 2 sensory neuropathy, an oxaliplatin dose reduction from 85 to 65 mg/m^2 was permitted"). These improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen.

The data demonstrate that liposomal irinotecan, when administered with oxaliplatin, 5-FU, and leucovorin according to claim 1, is able to treat metastatic adenocarcinoma of the pancreas in a first-line setting and provides more efficacious treatment than the current standard treatment described in Conroy, with acceptable tolerability and side effects.

Accordingly, as set forth above, there is no motivation to have combined the teachings of Bayever, Conroy, and Melis, and there would have been no reasonable expectation of success. While the right to present additional objective evidence of nonobviousness is reserved, Applicant

[4] Of the 32 patients in the pooled population of patients from Cohort B and the dose-expansion group, 29 had metastatic disease (i.e., stage IV) at initial treatment. *See* Wainberg presentation at slide 7 pooled patient population column and footnote c.

respectfully asserts that the evidence of unexpected results presented above negates any prima facie case of obviousness. Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 of claims 1, 5-8, 10 and 19 over Bayever, in view of Conroy, and in further view of Melis, as there is no prima facie case of obviousness.

Claims 4, 9, 18 and 23

The Examiner maintains the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. 103 as allegedly being unpatentable over Bayever, in view of Conroy, and further in view of Melis and further in view of Fleming et al. found at htttp://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-inchemotherapy-administration/article/378072/ ("Fleming"). Action at pages 6-7.

The Examiner alleges that Fleming, which is an opinion by one medical doctor, discloses "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." *See* Action at 7. Fleming, however, states "the best or correct order for drug administration is very difficult to answer" and acknowledges exceptions exist to the generalization the Examiner relies upon. Fleming indicates that, for example, in administering a taxane with a platinum (e.g., Taxol with carboplatin), the taxane should *always* be given first because "myelosupproession has been observed in patients who received the platinum before the taxane." *See* Fleming. Notably, Fleming does *not* mention any of the drugs in the claimed regimen, and does not speak to whether a need exists for well-defined sequence of administration or the interval between any of the claimed agents (including 5-FU and/or leucovorin[5]), or if any "published reports" exist for the claimed chemotherapy. Fleming also only mentions "half-life" as a basis for the generalization and does not discuss the physiological effects of chemotherapy drugs on their targets. Antineoplastic agents can have different mechanisms of action, activity, and vary in their effects on cell cycle and apoptosis, all of which may factor into determining whether an optimal sequence of their administration exists. As such, the relevance of Fleming to the instant

[5] Bayever at page 11 indicates leucovorin "increase[s] the binding of folate cofactor and active 5-FU with thymidylate synthetase," and is known to be administered *prior* to 5-FU.

application is limited as best. Applicant also respectfully traverses for the reasons discussed above, in the February 25, 2021 Final Office Action response, and in the January 7, 2020 Non-Final Office Action Response with respect to claims 1 and 19, from which claims 4, 9, 18, and 23 depend.

Accordingly, claims 4, 9, 18, and 23, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, leucovorin (200 mg/m^2 l-form or 400 mg/m^2 l+d form), and 2,400 mg/m^2 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, and/or Fleming. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. § 103 over Bayever in view of Conroy, and further in view of Melis and Fleming.

Rejection of claims 11-15 and 21-22

The Examiner maintains the rejection of 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 Melis, and as evidenced by WO 2016/094402 ("Bayever II"). Action at pages 8-9.

Applicant respectfully traverses for at least the reasons discussed above, in the February 25, 2021, Final Office Action response, and in the January 7, 2020, Non-Final Office Action Response with respect to claims 1 and 19, from which claims 11-15 and 21-22 depend. Accordingly, claims 11-15 and 21-22, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m2 liposomal irinotecan, 60 mg/m2 oxaliplatin, leucovorin (200 mg/m2 l-form or 400 mg/m2 l+d form), and 2,400 mg/m2 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, 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 Melis, and as evidenced by Bayever II.

III. Nonstatutory Double Patenting

U.S. Patent No. 9,492,442

The Examiner maintains the rejection of claims 1, 4-15, 18-19, and 21-23 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 Melis. Action at pages 11-12. The Examiner alleges that "[a]lthough the claims at issue are not identical, they are not patentably distinct from each other." The Examiner alleges the claims of the '442 Patent "recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin" and relies on Conroy and Melis for disclosing oxaliplatin. *Id.*

Claim 1 of the '442 patent recites:

> A method of treating an exocrine pancreatic cancer, the method comprising intravenously administering an antineoplastic therapy once every two weeks to a human patient having the exocrine pancreatic cancer, the antineoplastic therapy ***consisting of***:
>
> a. administering a 60-80 mg/m^2 dose of a liposomal irinotecan composition in a diluted irinotecan injection formulation to the human patient in a single infusion over about 90 minutes, the diluted irinotecan injection formulation comprising irinotecan liposomes in 500 mL of an injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition effective to deliver the dose of liposomal irinotecan, in combination with
>
> b. administering a therapeutically effective amount of leucovorin and 5-fluorouracil,
>
> to treat the exocrine pancreatic cancer in the patient, wherein the irinotecan liposome composition comprises phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposomes in the liposomal irinotecan composition have a diameter of approximately 80-140 nm.

Claims 10 and 19 of the '442 patent similarly recite "the antineoplastic therapy ***consisting of***" the "closed set" of the specifically listed regimen, which the Examiner acknowledges to ***not*** include administration of oxaliplatin. It is well known that "a double patenting rejection must

rely on a comparison with the *claims* in an issued patent or pending application." *See* MPEP § 804(III) (emphasis added). Here, the plain language of the claims of the '442 patent necessarily excludes the addition of oxaliplatin, in contravention of the Examiner's assertion that "it would have been prima facie obvious to use oxaliplatin in the issued method."

Applicant further submits that one of ordinary skill in the art would not combine the teachings of Conroy and Melis regarding oxaliplatin with the claims of the '442 Patent for the reasons set forth above regarding why a person of ordinary skill in the art would not combine the teachings of Bayever with Conroy and/or Melis, much less with a reasonable expectation of success, and further for the reasons set forth in the February 25, 2021, Final Office Action Response, and in the January 7, 2020 Non-Final Office Action Response. Claims 10-30 of the '442 Patent are further directed to second-line treatment, and the discussion above regarding why a person of ordinary skill in the art would not combine teachings regarding second-line therapy with teachings regarding first-line therapy apply here. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy. 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 Melis.

U.S. Patent No. 10,980,795

The Examiner rejects claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-15 of U.S. Patent No. 10,980,795 ("the '795 Patent"). *See* Action at page 12 (not citing any other references). The Examiner alleges that the claims "the claims in both said patent and instant claims are drawn to treating metastatic adenocarcinoma of the pancreas using the same composition."

Claim 1 of the '795 Patent recites:

> A method of treating metastatic adenocarcinoma of the pancreas in a human patient ***who has previously been treated with gemcitabine***, comprising

intravenously administering an antineoplastic therapy to the patient once every two weeks, the therapy ***consisting of***

i) irinotecan sucrose octasulfate salt liposome injection in a dose providing the equivalent of 70 mg/m^2 of irinotecan free base,

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

iii) 2400 mg/m^2 of 5-fluorouracil.

Claim 1 of the '795 Patent and its dependent claims also recite that the therapy "consists of" the specifically listed regimen, which does not include, and in fact necessarily excludes, the addition of oxaliplatin. The pending claims are not obvious variations of the claims of the '795 Patent for at least this reason.

Additionally, the claims of the '795 Patent recite "treating metastatic adenocarcinoma of the pancreas in a human patient *who has previously been treated with gemcitabine*," i.e., second line treatment. *See* '795 Patent at claim 1 (emphasis added). The claims of the '795 Patent would therefore not render the instant claims obvious for the reasons discussed above regarding second-line therapy versus the first-line treatment of the claims. To the extent the Examiner otherwise asserts the '795 claims would render the instant claims obvious in combination with Conroy and Melis, Applicant traverses for the reasons set forth above, and further for the reasons set forth in the February 25, 2021, Final Office Action Response, and in the January 7, 2020 Non-Final Office Action Response. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy. Accordingly, the pending claims are not obvious variations of issued claims 1-15 of the '795 Patent.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-15 of the '795 Patent, in view of Conroy, and further in view of Melis.

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 25, 2022

By: /Victoria S. Lee/
Victoria S. Lee
Reg. No. 70,240
McNeill Baur PLLC
(732) 704-3972

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:	Victoria SunHsuan-Chou Lee/Dawn MacPherson
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 - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
			Total in USD ($)	**1480**

Electronic Acknowledgement Receipt

EFS ID:	45086212
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:	Victoria SunHsuan-Chou Lee/Dawn MacPherson
Filer Authorized By:	Victoria SunHsuan-Chou Lee
Attorney Docket Number:	263266-421428
Receipt Date:	25-FEB-2022
Filing Date:	10-NOV-2017
Time Stamp:	14:13:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1480
RAM confirmation Number	E20222OE15423089
Deposit Account	506488
Authorized User	Dawn MacPherson

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	Extension of Time	2022-02-25_01208-0007-01US_EOT.pdf	149784 a05e56712bd2895dd0d52473bd885c1d2fc3886e	no	2
Warnings:					
Information:					
2		2022-02-25_01208-0007-01US_Response_to_NFOA_FINAL.pdf	238676 84723e0f2c46210d4473698ec4af8ce3f78786ff	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Request for Reconsideration-After Non-Final Rejection	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	21

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	38577 9025244a2b4f286a4453451259bf34ca0112241f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	427037		

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/AIA/22 (10-20)
Approved for use through 11/30/2020. 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: Gollamudi S. Kishore

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))	$220	$110	$55	$
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☑ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$ 1,480
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☐ 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 506488.

☑ 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 70,240.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Victoria S. Lee/ — Signature

February 25, 2022 — Date

Victoria S. Lee — Typed or printed name

732-704-3972 — 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.

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.
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.
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/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 $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ 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

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/25/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	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

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	PSA
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARY R HUNTER/
*** 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.	

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/Dawn MacPherson
Attorney Docket Number:	01208-0007-01US

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($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	45187021
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/Dawn MacPherson
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	01208-0007-01US
Receipt Date:	09-MAR-2022
Filing Date:	10-NOV-2017
Time Stamp:	16:04:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E202239G05272164
Deposit Account	506488
Authorized User	Dawn MacPherson

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	Fee Worksheet (SB06)	fee-info.pdf	38366 7e34f1db56efc1bcb0a287b4727ee9c670ff1cc3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	38366		

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/08a (01-22)
Approved for use through 05/31/2024. 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	1612
Examiner Name	Gollamundi S. KISHORE
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	11052079	B2	2021-07-06	Hong et al.	
	2	11071726	B2	2021-07-27	Fitzgerald et al.	

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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
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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]
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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	Gollamundi S. KISHORE
	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	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, including main request and auxiliary requests 1-3, 62 pages.	
	2	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D18 (WAINBERG Z, et al., "First-line Liposomal Irinotecan With Oxaliplatin, 5-Fluorouracil and Leucovorin (NALIRIFOX) in Pancreatic Ductal Adenocarcinoma: A Phase I/II Study," Eur J Cancer. 151:14-24 (2021)).	
	3	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D19 (Declaration of Dr. Bin Zhang, including Annex A and Annex B, 15 pages).	
	4	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D20 (EISENHAUER E, et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)," Eur J Cancer. 45 (2):228-47 (2009)).	
	5	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D21 (JANG G, et al., "Comparison of RECIST Version 1.0 and 1.1 in Assessment of Tumor Response by Computed Tomography in Advanced Gastric Cancer," Chin J Cancer Res. 25(6):689-694 (2013)).	
	6	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D22 (KIM J, et al., "Comparison of RECIST 1.0 and RECIST 1.1 in Patients with Metastatic Cancer: A Pooled Analysis," J Cancer. 6 (4):387-393 (2015)).	
	7	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D23 (Trial Protocol for CONROY T, et al., "FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer," N Engl J Med. 364 (19):1817-25 (2011), 88 pages).	
	8	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D24 (Package leaflet for Campto 20 mg/mL concentration for solution for infusion irinotecan hydrochloride, trihydrate, last revised May, 2021, 11 pages).	
	9	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, 17 pages.	
	10	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D25 (TSAI C, et al., "Nanovector-Based Therapies in Advanced Pancreatic Cancer," J Gastroint Oncol 2(3):185-94 (2011)).	

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	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

	11	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D26 (YOO C, et al., "A Randomised Phase II Study of Modified FOLFIRI.3 vs Modified FOLFOX as Second-Line Therapy in Patients with Gemcitabine-Refractory Advanced Pancreatic Cancer," Br J Cancer. 101(10):1658-63 (2009)).
	12	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D27 (KALRA A, et al., "Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion," Cancer Res. 74(23):7003-13 (2014)).
	13	EP3337478: Proprietor's Response to Sandoz AG's Submission of 1st February 2022, dated February 28, 2022, 17 pages.
	14	BRENDEL K, et al., "Population Pharmacokinetics of Liposomal Irinotecan in Patients With Cancer and Exposure–Safety Analyses in Patients With Metastatic Pancreatic Cancer," CPT Pharmacometrics Syst Pharmacol. 10 (12):1550-63, doi: 10.1002/psp4.12725 (2021).
	15	GEBAUER F, et al., "Study Protocol of an Open-Label, Single Arm Phase II Trial Investigating the Efficacy, Safety and Quality of Life of Neoadjuvant Chemotherapy With Liposomal Irinotecan Combined With Oxaliplatin and 5-Fluorouracil/Folinic Acid Followed by Curative Surgical Resection in Patients With Hepatic Oligometastatic Adenocarcinoma of the Pancreas (HOLIPANC)," BMC Cancer. 21(1):1239, doi: 10.1186/s12885-021-08966-3, pages 1-11 (2021).
	16	GEORGE B, et al., "The Association of Real-World CA 19-9 Level Monitoring Patterns and Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma," Front Oncol. 11:754687, doi: 10.3389/fonc.2021.754687, pages 1-8 (2021).
	17	PAZ-ARES L, et al., "RESILIENT Part 1: A Phase 2 Dose-Exploration and Dose-Expansion Study of Second-Line Liposomal Irinotecan in Adults With Small Cell Lung Cancer," Cancer. doi: 10.1002/cncr.34123, online ahead of print, pages 1-11 (2022).
	18	SACHDEV J, et al., "Phase I Study of Liposomal Irinotecan in Patients With Metastatic Breast Cancer: Findings from the Expansion Phase," Breast Cancer Res Treat..185(3):759-71 (2021), Epub 2020.
	19	TOMICKI S, et al., "Real-World Cost of Care for Commercially Insured Versus Medicare Patients With Metastatic Pancreatic Cancer Who Received Guideline-Recommended Therapies," Am Health Drug Benefits. 14(2):70-78 (2021).
	20	YOO C, et al., "Liposomal Irinotecan Plus Fluorouracil and Leucovorin Versus Fluorouracil and Leucovorin for Metastatic Biliary Tract Cancer After Progression on Gemcitabine Plus Cisplatin (NIFTY): A Multicentre, Open-Label, Randomized, Phase 2b Study," Lancet Oncol. 22(11):1560-1572, doi: 10.1016/S1470-2045(21)00486-1, pages 1-13 (2021).
	21	YU K, et al., "Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma Treated With Liposomal Irinotecan," Front Oncol. 11:678070. doi: 10.3389/fonc.2021.678070, pages 1-9 (2021).

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	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

	22	YU K, et al., "Real-World Prognostic Factors for Survival Among Treated Patients With Metastatic Pancreatic Ductal Adenocarcinoma," Cancer Med. 10(24):8934-43 (2021).
	23	U.S. Patent Application No. 15/664,976: 2021-04-21 Notice of Allowance including Examiner's Reasons for Allowance, 14 pages.
	24	U.S. Patent Application No. 15/809,815: 2021-08-26 Non-Final Office Action, 14 pages.
	25	U.S. Patent Application No. 16/012,351: 2021-03-08 Notice of Allowance including Examiner's Reasons for Allowance, 9 pages.
	26	U.S. Patent Application No. 16/012,372: 2021-02-11 Notice of Allowance including Examiner's Reasons for Allowance, 9 pages.
	27	U.S. Patent Application No. 16/302,050: 2021-08-11 Non-Final Office Action, 17 pages.
	28	U.S. Patent Application No. 16/567,902: 2021-03-08 Notice of Allowance including Examiner's Reasons for Allowance and Examiner Interview Summary, 22 pages.
	29	U.S. Patent Application No. 16/711,072: 2021-12-10 Non-Final Office Action, 19 pages.
	30	U.S. Patent Application No. 16/906,601: 2022-01-07 Non-Final Office Action, 21 pages.

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.

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	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

[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	Eliel Bayever
	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	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)	2022-03-09
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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Electronic Acknowledgement Receipt

EFS ID:	45186168
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/Dawn MacPherson
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	01208-0007-01US
Receipt Date:	09-MAR-2022
Filing Date:	10-NOV-2017
Time Stamp:	15:53:29
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	Transmittal Letter	2022-03-09_01208-0007-01US_IDS_Transmittal.pdf	134154 2f0c6259e0fcaed29ad2692d3d5d6f009ef4b2e6	no	2

Warnings:

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2	Non Patent Literature	EP3337478_Opp_Resp_incl_MR_AR1-AR3.pdf	4318390 02e6b60a49660b2940282f494d229a7649b83db3	no	62
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3	Non Patent Literature	EP3337478_Opp_Resp_D18_Wainberg_2021.pdf	1215486 fc0d93bd3b8c332812919e87a087e0762d353eab	no	11
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9	Non Patent Literature	EP3337478_Opp_Resp_D24_Campto_leaflet.pdf	508806 3ce5ec326d641dd9f6f7c21deb172d5151f95e46	no	11
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26	Non Patent Literature	US16012351_2021-03-08_NOA.pdf	479099 2d9be8db93c610911a107320421b8d06fb7258fc	no	9
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28	Non Patent Literature	US16302050_2021-08-11_OA.pdf	671471 aabec30bab3ded7ed29963f289d3d1aed1cf24b6	no	17
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29	Non Patent Literature	US16567902_2021-03-08_NOA_Int_Sum.pdf	1007708 8b174291388c48f47876c4ae6b6e45b181537fff	no	22
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31	Non Patent Literature	US16906601_2022-01-07_OA.pdf	927401 a87db78cff5d71d6f79109d91e86e96d4cc32357	no	21
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32	Information Disclosure Statement (IDS) Form (SB08)	2022-03-09_01208-0007-01US_SB08a.pdf	1284907 b1a1c462a1fa5412bba6dacc2c347eece0bc7289	no	7
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New Applications Under 35 U.S.C. 111

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1612
Eliel BAYEVER et al.	
Application No.: 15/809,815	Examiner: Gollamudi S. Kishore
Filed: November 10, 2017	Confirmation No.: 5137
For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

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

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 document 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 $260, as required by 37 C.F.R. §1.97(c).

Copies of the non-US patent publication documents are 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: March 9, 2022

By: /Mary R. Henninger/
Mary R. Henninger
Reg. No. 56,992
404-891-1400

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European Patent Office
80298 Munich
Germany

Electronically submitted

Your Ref 16758337.6 - 1112 / 3337478
Our Ref O008382EP:ECO/FJT/HAB
Date 7th December 2021

Dear Opposition Division,

Re: European Patent No. 3337478
In the name of IPSEN BIOPHARM LTD.

The proprietor's response to the oppositions is enclosed.

As explained in the enclosed, the proprietor's Main Request is for the patent to be maintained on the basis of the enclosed set of claims labelled "Main Request – December 2021". If the Main Request cannot be allowed, the proprietor requests that the patent be maintained on the basis of one of Auxiliary Requests 1-3, also enclosed.

Oral proceedings are requested should the Opposition Division be considering allowing anything other than the proprietor's Main Request.

Yours faithfully,

// ELECTRONICALLY SIGNED AND SUBMITTED //

OATES, Edward Christopher
Carpmaels & Ransford LLP Professional Association No. 182

Encl. Proprietor's response to oppositions
Main Request (clean and marked-up)
Auxiliary Requests 1-3 (clean and marked-up)
D18-D24

Europäisches Patentamt
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Submission in opposition proceedings

Representative:

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- representing the proprietor(s):	IPSEN BIOPHARM LTD.
Proprietor/representative's reference	O008382EP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP3337478
Application No.	EP16758337.6
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	12 August 2020
Title of the invention	Drug combination comprising liposomal irinotecan, oxaliplatin, 5-fluorouracil and leucovorin for treating metastatic pancreatic cancer
Proprietor of the patent	IPSEN BIOPHARM LTD.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Reply of the patent proprietor to the notice(s) of opposition	O008382EP-OPP-Opposition statement-f1237800 final - 7th Dec.pdf	OBSO3.pdf
2	Main request in opposition	Main Request (clean).pdf	MAINREQ-1.pdf
3	Main request in opposition	Main Request (tracked).pdf	MAINREQ-2.pdf
4	Auxiliary request in opposition	AR 1 (clean).pdf	AUXREQ-1.pdf
5	Auxiliary request in opposition	AR 1 (tracked).pdf	AUXREQ-2.pdf
6	Auxiliary request in opposition	AR 2 (clean).pdf	AUXREQ-3.pdf
7	Auxiliary request in opposition	AR 2 (tracked).pdf	AUXREQ-4.pdf
8	Auxiliary request in opposition	AR 3 (clean).pdf	AUXREQ-5.pdf
9	Auxiliary request in opposition	AR 3 (tracked).pdf	AUXREQ-6.pdf
10	Any annexes (other than citation) to an opposition	O008382EP-O-Letter-2ee09fbe	OTHER-1.pdf

	letter - Covering letter	(signed).pdf	

Evidence filed subsequently:

D18	Other evidence	D18 - Wainberg original file name: D18 - Wainberg.pdf attached as: Other-evidence-1.pdf
D19	Other evidence	D19 - Zhang declaration original file name: D19 - Zhang declaration.pdf attached as: Other-evidence-7.pdf
D20	Other evidence	D20 - Eisenhauer original file name: D20 - Eisenhauer.pdf attached as: Other-evidence-2.pdf
D21	Other evidence	D21 - Jang original file name: D21 - Jang.pdf attached as: Other-evidence-3.pdf
D22	Other evidence	D22 - Kim original file name: D22 - Kim.pdf attached as: Other-evidence-4.pdf
D23	Other evidence	D23 - Protocol supplementary materials of D10 original file name: D23 - Protocol supplementary materials of D10.pdf attached as: Other-evidence-5.pdf
D24	Other evidence	D24 - Package leaflet for Campto original file name: D24 - Package leaflet for Campto.pdf attached as: Other-evidence-6.pdf

Payment

1	Method of payment	Not specified
	Currency:	EUR

Signatures

Place:	**London**
Date:	**07 December 2021**
Signed by:	**/OATES, Edward Christopher/**
Association:	**Carpmaels & Ransford LLP**
Representative name:	**Edward Christopher OATES**
Capacity:	**(Representative)**

PROPRIETOR'S SUBMISSIONS IN RESPONSE TO OPPOSITIONS

EUROPEAN PATENT 3 337 478 B1

IN THE NAME OF IPSEN BIOPHARM LTD.

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1 INTRODUCTION AND REQUESTS

1.1 European patent EP 3 337 478 ("the patent") owned by Ipsen Biopharm Ltd. ("the proprietor") has been opposed by two parties: Sandoz AG – Opponent 1 ("O1") and Generics [UK] Limited – Opponent 2 ("O2"). This is the proprietor's response to the oppositions.

1.2 The proprietor's Main Request is that the patent be maintained on the basis of the enclosed Main Request claims.

1.3 In the Main Request claims, the granted claims have been amended in response to the inventive step attacks from the opponents by strengthening their priority entitlement. In particular, granted claims 1, 6 and 9 are amended so that liposomal irinotecan is now defined as "irinotecan sucrose octasulfate salt liposome injection". Basis for this amendment is found on page 15, line 24 of the application as filed, as well as page 27, line 20 of the application as filed. Dependent claims 2, 11, 13, and 14 from the claims as granted are deleted, and the remaining dependent claims are re-numbered.

1.4 In the alternative, the proprietor requests that the patent be maintained on the basis of one of the enclosed Auxiliary Requests 1-3, which are described in section 6 below.

1.5 The proprietor requests oral proceedings if the Opposition Division ("OD") is considering not allowing the Main Request.

1.6 The proprietor requests permission to make further amendments to the Main and Auxiliary Requests, and/or to submit further auxiliary requests in future in response to points raised by the opponents or the OD (e.g., by deleting dependent claims).

1.7 Should the OD deem amendment to the description necessary, the proprietor requests that any such amendment be deferred until final agreement on the claims has been reached.

1.8 For the avoidance of doubt, any unclaimed or deleted subject matter is not abandoned.

2 DOCUMENTS ENCLOSED

2.1 The proprietor files the following documents:

- D18 – "First-line liposomal irinotecan with oxaliplatin 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study", European Journal of Cancer, 151 (2021), 14 – 24, Wainberg et al.
- D19 – Declaration of Dr. Bin Zhang
- D20 – "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)", European Journal of Cancer, 45 (2009), 228 – 247, Eisenhauer et al.

- D21 – "Comparison of RECIST v1.0 and 1.1 in assessment of tumor response by computed tomography in advanced gastric cancer", Chin J Cancer Res, 2013, 25(6), 689 – 694, Jang et al.
- D22 – "Comparison of RECIST 1.0 and RECIST 1.1 in Patients with Metastatic Cancer: A Pooled Analysis", Journal of Cancer 2015, 6(4), 387 – 393, Kim et al.
- D23 – Protocol supplementary materials (FR) of D10
- D24 – "Package leaflet: Information for the user, Campto 20 mg/mL concentrate for solution for infusion"

2.2 D18 and D19 are filed in response to opponents' allegations that the claimed invention does not show an improvement over the prior art. D20-D22 are filed in support of the technical effect demonstrated in D18 and D19. D23 and D24 are filed as evidence in support of the distinguishing features between the claimed invention and D10.

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3 SUMMARY OF THE INVENTION

3.1 The claimed invention is embodied by the medicinal product Onivyde®, which has irinotecan sucrose octasulfate salt liposome injection as its active ingredient. Onivyde® was known for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy, i.e. as a second-line treatment, in combination with 5-fluorouracil (5-FU) and leucovorin (LV)[1]. By contrast, the claimed invention relates to the use of irinotecan sucrose octasulfate salt liposome injection in treating patients who have not previously received chemotherapy to treat their metastatic adenocarcinoma of the pancreas, i.e. as a first-line treatment.

3.2 The treatment of pancreatic cancer presents significant challenges for numerous reasons: it is typically detected at a late stage, generally has a very poor prognosis, and is characterised by aggressive metastasis. It is the fourth leading cause of cancer death in the USA, and has a 5-year survival rate of only 6%. Moreover, as discussed in paragraph [0002] of the patent, the incidence of pancreatic cancer is increasing, and it is set to become the second-leading cause of cancer-related death by 2030. This, as well as the nature of the disease in producing few early symptoms resulting in common late diagnosis, means that there is a strong desire for improved, and additional, treatment options for patients.

3.3 Known first-line treatments of metastatic adenocarcinoma of the pancreas include gemcitabine-based therapies and the FOLFIRINOX (5-fluorouracil/leucovorin + (non-liposomal) irinotecan + oxaliplatin) regimen (see D10, for example). The former is discussed on page 853 of D3 where their clinical benefit is described as "marginal" or "of uncertain impact on quality of life". The latter, as discussed in paragraph [0003] of the patent, is known to have significant toxicity issues, and its use is limited to patients with better performance status. Thus, there remains a significant unmet clinical need for improved, efficacious, and safe first-line treatments of this disease.

[1] The FDA approval relating the second-line treatment of metastatic adenocarcinoma of the pancreas with Onivyde® is discussed in D4.

3.4 The present invention relates to exactly that: by way of the data presented in the patent, particularly in Example 4, as well as the results of a clinical study of the claimed regime ("NALIRIFOX", see D18), improvements in efficacy over the FOLFIRINOX therapy have been shown, and a sufficiently safe treatment has been provided.

3.5 This regimen is defined in claim 1 of the Main Request by a combination of four specific drugs: irinotecan sucrose octasulfate salt liposome injection, oxaliplatin, leucovorin and 5-fluorouracil. Each drug has a specific, defined dosage and is dosed a total of once every two weeks. The condition treated is metastatic adenocarcinoma of the pancreas in human patients that have not previously received chemotherapy to treat the condition.

3.6 The claims of the Main Request are structured such that claims 5 and 8 do not contain an explicit reference to claim 1. However, these claims each recite every feature of claim 1. Therefore, these claims are *de facto* dependent claims, along with claims 2-4, 6, 7, and 9-12. Accordingly, the sole independent claim in the Main Request is claim 1.

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4 PRIORITY

4.1 O1 has alleged that the claims are not entitled to any of the claimed priority dates. O2 mentions that it endorses this allegation, although it does not provide any arguments of its own. The proprietor disagrees: the first priority document, US 62/208,209 (hereafter P1), which was filed on 21st August 2015, relates to the "same invention" as in claim 1 of the Main Request, meaning that the patent validly claims its earliest priority date.

The subject matter of claim 1 has basis in P1

4.2 Claim 1 of the Main Request is formatted as an EPC-2000 medical use claim which refers to an antineoplastic therapy which is a combination of active ingredients in specific dosages, for a specific patient population, and may be summarised as follows:

Drugs and doses:	irinotecan sucrose octasulfate salt liposome injection – 60 mg/m^2
	oxaliplatin – 60 mg/m^2
	leucovorin – 200 mg/m^2 of (l)-form, or 400 mg/m^2 of (l+d) racemic form
	5-fluorouracil – 2,400 mg/m^2
Condition treated:	Metastatic adenocarcinoma of the pancreas
Patient treated:	Human patient, not having previously received chemotherapy to treat the condition
Dosing frequency:	Combination administered once every two weeks

4.3 The same invention as claim 1 is disclosed in P1 and the subject matter of claim 1 is directly and unambiguously derivable from P1, taking into account features implicit to the skilled person in what is expressly mentioned in P1 (i.e. the gold standard test, an assessment that

is identical to the test required for compliance with Article 123(2) EPC)[2]. Two alternative approaches are available to derive basis for claim 1 in P1: starting from claim 1 of P1, and starting from claim 22 of P1. Both of these derivations demonstrate that the priority claim to P1 is valid.

Claim 1 is derivable from claim 1 of P1

4.4 Claim 1 of P1 is:

> 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.

4.5 Paragraph [0006] on page 2 of P1 provides direct and unambiguous disclosure that "MM-398 liposomal irinotecan" is "irinotecan sucrose octasulfate salt liposome injection" as required by claim 1 of the Main Request.

4.6 Claims 18-20 of P1 provide a direct and unambiguous disclosure of the specific pancreatic cancer treated in claim 1 – metastatic adenocarcinoma of the pancreas:

> 18. The method any one of claims 1-18, wherein the pancreatic cancer is adenocarcinoma of the pancreas.
> 19. The method of claim 18, wherein the pancreatic cancer is unresectable, locally advanced or metastatic adenocarcinoma of the pancreas.
> 20. The method of claim 19, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas.

4.7 The fact that metastatic adenocarcinoma of the pancreas is in its own dependent claim confirms unambiguously that treatment of metastatic adenocarcinoma of the pancreas represents a preferred embodiment of the invention disclosed in P1. Further support for this may be found in P1 in paragraph [0015], final sentence; paragraph [0035]; and the inclusion criteria for the Phase II study disclosed in Example 1 (paragraph [00136]).

4.8 Claim 3 of P1 provides basis for the remaining components used in the combination therapy (oxaliplatin, leucovorin and 5-fluorouracil):

> 3. The method of claim 1, wherein the MM398 liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil to treat the pancreatic cancer in the human subject.

4.9 The four sole components of the combination therapy constitute the antineoplastic therapy in claim 1, which is supported throughout the description of P1, particularly paragraphs [0006] and [0063].

[2] Guidelines for Examination 2021, F-VI-2.2, and G 2/98

4.10 Claims 4 and 5 of P1 respectively disclose a range of about 60 to about 80 mg/m^2 of liposomal irinotecan, and the two preferred values at the endpoint of this range, 60 mg/m^2 and 80 mg/m^2 of liposomal irinotecan:

> 4. The method of any one of claims 1-3, wherein the amount of MM-398 liposomal irinotecan administered is from about 60 mg/m^2 to about 80 mg/m^2.
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> 5. The method of claim 4, wherein the amount of MM-398 liposomal irinotecan administered is administered is 60 mg/m^2 or 80 mg/m^2.

4.11 A similar disclosure is found in paragraph [0077] of P1. Thus, these passages of P1 demonstrate that a liposomal irinotecan dosage of 60 mg/m^2 represents a preferred embodiment of the invention disclosed in P1.

4.12 Claims 7 and 8 of P1 respectively disclose a range of about 60 mg/m^2 to about 85 mg/m^2 of oxaliplatin, and the three preferred values in this range, 60 mg/m^2, 75 mg/m^2 and 85 mg/m^2:

> 7. The method of claim 6, wherein the amount of oxaliplatin administered is from about 60 mg/m^2 to about 85 mg/m^2.
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> 8. The method of claim 7, wherein the amount of oxaliplatin administered is 60 mg/m^2, 75 mg/m^2, or 85 mg/m^2.

4.13 Likewise, claims 7 and 8 of P1 demonstrate that a dosage of 60 mg/m^2 oxaliplatin represents a preferred embodiment of the invention disclosed in P1. Further confirmation that 60 mg/m^2 oxaliplatin is a preferred value is found in claim 22.

4.14 Yet further confirmation that the **combination** of 60 mg/m^2 of liposomal irinotecan and 60 mg/m^2 of oxaliplatin represents a preferred feature of P1 comes from the dose escalation in Example 1, specifically Table 7 in paragraph [00288] on pages 59-60. In this table, Dose level "-1" requires the administration of 60 mg/m^2 of liposomal irinotecan and 60 mg/m^2 of oxaliplatin, and also requires the administration of the 5-FU and leucovorin at doses which are identical to those required by claim 1. This table therefore provides a clear pointer towards a 60 mg/m^2 dose of both liposomal irinotecan and oxaliplatin.

4.15 Claims 9 and 12 provide the same dosages of leucovorin and 5-fluorouracil as in claim 1:

> 9. The method of any one of claims 1 to 8, 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.
>
> 12. The method of any one of claim 1-11, wherein the amount of 5-fluorouracil administered is 2,400 mg/m^2.

4.16 Treatment "once every two weeks" is disclosed in the penultimate sentence in paragraph [0075] of P1, where administration of the treatment "beginning on day 1 of a 2-week cycle wherein the method may include one or multiple cycles" is described[3]:

> days or every 28 days. In various embodiments, the MM-398 liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil are administered to the patient with metastatic cancer not previously treated with a chemotherapeutic agent in the metastatic setting beginning on day 1 of a 2-week cycle wherein the method may include one or multiple cycles. In some of these

4.17 This dosing frequency is disclosed as being applicable to all of the embodiments disclosed in P1. This frequency is the only suggested frequency in the examples. For example, paragraph [00365] mentions this frequency in both arms of Example 1. As held in T 197/08, reasons 3.3, because this feature is present in each of the examples, this indicates that this feature represents a preferred embodiment when considering the application of Article 123(2) EPC, and by extension Article 76(1) EPC.

4.18 Thus, claim 1 represents a combination of features which are said to be preferred in P1. A combination of preferred features cannot generate new subject matter because such a combination is evidently the best way of achieving the technical effects that the invention aimed to provide for[4].

4.19 Thus, claim 1 has basis starting from claim 1 of P1, meaning that the same invention is disclosed, and Article 76(1) EPC is fulfilled.

Claim 1 is derivable from claim 22 of P1

4.20 Alternatively, claim 1 can be derived directly and unambiguously from claim 22 of P1:

> 22. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the adenocarcinoma, the method comprising intravenously administering to the patient 80 mg/m^2 of MM-398 liposomal irinotecan, 60 or 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.

4.21 Claim 22 of P1 differs from claim 1 in only four ways: it specifies "intravenously" administering the combination, it refers to a dosage of "80 mg/m^2" instead of "60 mg/m^2" of liposomal irinotecan, it does not specify that the combination is administered "once every two weeks", and it does not refer to "irinotecan sucrose octasulfate salt liposome injection". For the final difference, direct and unambiguous basis is provided in paragraph [0006] of P1, as discussed above in section 4.5.

[3] Whilst this does not recite the *exact* wording "once every two weeks", the OD will be aware that literal support is not required – Guidelines for Examination 2021, G-IV-2.2. In addition, the disclosure in this passage of P1 amounts to an identical technical disclosure; the fixing of the treatment as being "on day 1 of a 2-week cycle" simply labels, without any technical significance, the start of a time period, which is implicitly defined by "once every two weeks" in claim 1, and the "one or multiple cycles" is identical to what is meant by "once every two weeks", in that any number greater than one, two-week cycle is covered by the claim. Therefore, the difference in wording is immaterial to the fact that a once every two-week frequency is directly and unambiguously disclosed in P1.
[4] See, e.g., T 68/99 and T1420/11.

4.22 The absence of "intravenously" in claim 1 constitutes an allowable removal of a feature from a claim, because the requirements of the test laid out in Guidelines for Examination 2021, H-V,3.1 are met:

- P1 does not state that "intravenous" administration is essential. For example, it is not a requirement of claim 1 in P1. It is discussed in connection with specific embodiments (paragraphs [0010]-[0013] of P1), and is merely exemplary as means of administering the dosage in paragraph [0040] of P1.
- The skilled person would directly and unambiguously recognise that the feature is not, as such, indispensable for the function of the invention in light of the technical problem the invention serves to solve. As discussed in detail below, the technical problem solved by the invention (the provision of a more efficacious treatment of metastatic adenocarcinoma of the pancreas in patients that have not previously received chemotherapy for this condition which is acceptably safe and tolerable) is not impacted by the presence or absence of intravenous administration in the claim.
- There is no necessary modification of any other feature to "compensate" for the change – the deletion simply does not alter the core invention of the claims at all.

4.23 Likewise, replacing 80 mg/m^2 of liposomal irinotecan in claim 22 of P1 with 60 mg/m^2 of liposomal irinotecan is an allowable replacement of a feature contemplated by the disclosure of P1. As discussed above, the 60 mg/m^2 dosage is disclosed at numerous points in P1, and nothing in P1 contemplates the specific dosage of 80 mg/m^2 of liposomal irinotecan as being essential. At worst for the proprietor, dependent claim 5 in P1 provides for both the 60 mg/m^2 and 80 mg/m^2 dosages as being equally preferred alternatives, and other passages of P1 go further and make it clear that the *combination* of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin (which appears in claim 22 of P1) represents a preferred embodiment of the invention disclosed in P1.

4.24 The "once every two weeks" feature is discussed in detail in 4.166 to 4.17, and for the same reasons given above this preferred feature is disclosed in combination with claim 22 in P1.

4.25 Thus, claim 1 also has basis starting from claim 22 of P1, meaning that the same invention is disclosed, and Article 76(1) EPC is fulfilled.

None of O1's arguments call compliance with Article 76(1) EPC into question

4.26 O1 suggests that, starting from claim 1 in P1, a number of selections are required in order to arrive at claim 1. O1 does not elaborate on exactly which features it believes need to be "selected". Nevertheless, as is outlined above, the features of claim 1 are all disclosed as being preferred features in P1, and P1 provides at least a pointer to combine these features. In any case, as discussed in 4.18 above, a combination of preferred features cannot generate new subject matter because such a combination is necessarily the best way to work the invention[5]. Therefore claim 1 is fully supported by P1.

[5] *Ibid.* 4.

4.27 The discussion in 4.1.5 of O1's opposition regarding different types of pancreatic cancers ignores the overall disclosure of P1, because not only is metastatic adenocarcinoma of the pancreas singled out in its own dependent claim (claim 20), it is also the focus of the clinical trial example in P1 – see paragraph [00112], for example. Therefore, any suggestion that, for example, the therapeutic indication in claim 1 must be selected from P1 must fail.

4.28 O1 also alleges that there is a "clear preference" for the combination therapy involving 80 mg/m^2 of liposomal irinotecan over the 60 mg/m^2. O1 suggests that the reduced dose should only be used in certain specific circumstances, referring to paragraph [0080] of P1 (which the proprietor understands should refer to paragraph [0081] of P1). This is plainly not what this paragraph states: it simply states that in "a particular embodiment", i.e. one embodiment where the patient is homozygous for the UGT1A1*28 allele, the dosage is at 60 mg/m^2. Patients homozygous for the UGT1A1*28 allele are not the "only" patients that may receive the 60 mg/m^2 dose. As outlined above, a large number of passages of P1 refer to a 60 mg/m^2 liposomal irinotecan without stating, implicitly or explicitly, that this dose should be administered only to patients who are homozygous for UGT1A1*28 allele. Thus, there is no basis for O1's suggestion that this dose is only disclosed in the context of treating a patient that is homozygous for UGT1A1*28 allele. As mentioned above in 4.14, the fact that this dose was being investigated in the dose escalation part of the study confirms that it represents a preferred embodiment.

4.29 The discussion in O1's arguments of the administration frequency did not take into account the direct and unambiguous disclosure of this feature in paragraph [0075] of P1. Therefore, O1's arguments in section 4.2 are irrelevant.

4.30 Finally, claim 1 as amended refers to "irinotecan sucrose octasulfate salt liposome injection". Therefore, O1's assertions about any difference between "MM-398 liposomal irinotecan" and "liposomal irinotecan" are not relevant.

Conclusion on priority

4.31 In view of the above explanation, claims 1-11 of the Main Request are all entitled to the priority date of P1, and therefore the effective date for assessing novelty and inventive step of the Main Request is the filing date of P1, 21st August 2015.

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5 INVENTIVE STEP

5.1 Both opponents' sole attacks against the patentability of the claims are lack of inventive step attacks under Article 56 EPC. Attacks based on two distinct starting points are raised, and can be summarised as follows:

- D3[6], D10[7] or D11[8], which relate to the FOLFIRINOX combination therapy and which have a publication date before the earliest priority date, are the closest prior art.

[6] O1 and O2.
[7] O2 only.
[8] O2 only.

O1 and O2 both consider the technical problem to be the provision of an alternative treatment of metastatic adenocarcinoma of the pancreas (in patients not having previously received chemotherapy for this condition).

Based on this technical problem, O1 and O2 consider the claimed solution to be obvious.

O1 argues obviousness based at the PCT filing date on the basis that the claims are not entitled to the P1 priority date (with O2 endorsing O1's arguments), and O2 argues obviousness based at the P1 priority date.

– D1 or D6, which have a publication date after the P1 priority date, can be the closest prior art on the basis that the claims are allegedly not entitled to the P1 priority date. D1 and D6 both relate to a Phase II study protocol for two different experimental drug combination therapies, both involving a nanoliposomal irinotecan.

O1 argues that the technical problem is the confirmation of a safe treatment of metastatic adenocarcinoma of the pancreas.

Based on this technical problem, O1 considers the claimed solution to be obvious.

5.2 As outlined above, the claims are entitled to the earliest priority date. Therefore, the second attack must fail, because it relies on closest prior art documents which are not prior art. Further, O1's first attack based at the PCT filing date must also fail for the same reason. However, in the event that the OD disagrees with the proprietor that the claims are entitled to the P1 priority date, the proprietor has set out its arguments on why the claims are inventive in any case.

5.3 The proprietor will set out first why the claims are inventive at the P1 priority date.

Inventive step at the P1 priority date

5.4 O1 refers in its arguments to, *inter alia*, D1, D4, D5, D6, D7 and D8, all of which were published after the P1 priority date. Thus, these documents were not available to the skilled person at the priority date and therefore should not be used for the assessment of inventive step under Article 56 EPC[9].

5.5 Therefore, in addition to D3, D10 and D11 (discussed already above), the only cited documents available to the skilled person at the P1 priority date are D2, D9, and D12-D17.

Analysis of closest prior art

5.6 O1 treats D3 as the closest prior art, whereas O2 treats either of D3, D10 or D11 as the closest prior art.

[9] Nevertheless, the contents of D4, D5 and D7, which O1 erroneously considers to be common general knowledge at the priority date, are discussed in detail below: these documents still do not render the claims obvious.

5.7 Each of D3, D10 and D11 discusses the PRODIGE 4/ACCORD 11 trial, which was a phase III study investigating the FOLFIRINOX regime as a first-line treatment for metastatic pancreatic adenocarcinoma.

5.8 D10, which was the initial disclosure reporting on this trial, is an appropriate closest prior art document. It is the source document for the discussion of the FOLFIRINOX trial in D3 (reference 6, see the paragraph bridging pages 853-854), and likewise for D11 (reference 1, discussed variously, including in the first sentence of the introduction on page 23). D10 provides the most complete discussion of the FOLFIRINOX therapy in treating the same condition as the claims, with results on both efficacy and safety. D10 thus represents the most promising starting point.

5.9 In addition, D10 relates to the same purpose or effect as the claims, i.e. the provision of a first-line treatment for metastatic pancreatic cancer (specifically adenocarcinoma) – see at least the background in the abstract (page 1817), and the "Patients" section under methods (page 1818)[10]. As mentioned, D10 relates to the FOLFIRINOX regime, and the dosage of this regime is described in the methods section of the abstract (page 1817) as follows[11]:

Drugs and doses:	**(non-liposomal)** irinotecan[12] – **180 mg/m²**
	oxaliplatin – **85 mg/m²**
	leucovorin – 400 mg/m²
	5-fluorouracil – **400 mg/m² bolus, followed by** 2,400 mg/m²
Condition treated:	Metastatic adenocarcinoma of the pancreas
Patient treated:	Human patient, not previously treated with chemotherapy for the condition
Dosage frequency:	Combination administered a total of once every two weeks

5.10 The results in D10 show that FOLFIRINOX was "an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma"[13].

5.11 Therefore, D10 is an appropriate closest prior art.

Distinguishing features and technical effects

5.12 The **distinguishing features** between D10 and the claims are as follows[14]:

[10] D10 meets all of the criteria set out in Guidelines for Examination 2021, G-VII-5.1 to qualify as the closest prior art.
[11] Parts of the D10 regimen which differ to the claims of the patent are shown in **bold**.
[12] Whilst it is not stated explicitly in D10, the non-liposomal irinotecan was administered in the form of irinotecan hydrochloride trihydrate. This is evidenced in D10's "protocol" document, i.e. supplementary information, enclosed as D23, which shows that the FOLFIRINOX treatment used irinotecan in the form of the medicinal product Campto® (see page 13/36, as numbered). D24, a packaging insert for Campto®, shows on page 1 that the active ingredient in Campto® is "irinotecan hydrochloride, trihydrate".
[13] See first sentence of "Discussion" section on page 1822 of D10.
[14] See D10, page 1819, "Treatment", first paragraph.

- The claims use **60 mg/m² liposomal irinotecan**, which is **irinotecan sucrose octasulfate salt liposome injection**, whereas D10 discloses only **non-liposomal** irinotecan[15] at a dose of **180 mg/m²**.
- The claims use **60 mg/m²** oxaliplatin whereas D10 discloses **85 mg/m²** oxaliplatin.
- The claims use **2,400 mg/m²** in total 5-fluorouracil whereas D10 discloses the use of a higher dose of **2,800 mg/m²** total 5-fluoruracil, by way of a 400 mg/m² bolus of 5-fluorouracil before a 2,400 mg/m² administration.

5.13 The **technical effect** resulting from these differences is the provision of a **more efficacious** treatment of metastatic adenocarcinoma of the pancreas (in patients that have not previously received chemotherapy for this condition), that is acceptably safe and tolerable. Evidence of this technical effect is provided in the patent, as well as in D18 and D19.

5.14 Providing an improvement over the known FOLFIRINOX regimen (i.e. the regimen used in D10) was a problem already contemplated in the patent when filed. In paragraph [0003] of the background section on page 2 of the patent, the FOLFIRINOX regimen is discussed, as well as its associated downsides. Improving the efficacy of the FOLFIRINOX regimen, as well as its safety and tolerability, is also discussed in paragraph [0059] on page 16 of the patent, in terms of the aim of the Phase 2 study which is the subject of Examples 3 and 4 of the patent:

> *"In the study, MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen."*

5.15 An animal model comparison of FOLFIRINOX and a regimen using the irinotecan sucrose octasulfate salt liposome injection required by claim 1 is also disclosed in the patent (see paragraphs [0015]-[0017] on page 8 with reference to Figure 3B[16]). In this animal model, the irinotecan sucrose octasulfate salt liposome injection performed better than non-liposomal irinotecan hydrochloride trihydrate at equivalent exposure doses of irinotecan. In particular, significantly more tumour growth inhibition is observed for the regimen containing nal-IRI (crosses in Fig. 3B) versus the non-liposomal irinotecan (asterisks in Fig. 3B), following treatment.

5.16 The patent provides further data by way of at least Figures 5A, 5C, 6B, 7 and 8 in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model, providing support that a dosage regimen with irinotecan sucrose octasulfate salt liposome injection according to claim 1, oxaliplatin and 5-FU showed significantly reduced tumour volume percent change compared to the non-liposomal irinotecan combination (see paragraphs [0020]-[0023] on pages 8-9 of the patent)[17]. This combination of drugs provided the largest inhibition of tumour growth of those tested, and the mice treated with this therapy ("NAPOX")

[15] *Ibid.* 12.
[16] See paragraph [0017]: "However, comparison of [...] 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."
[17] N.B. although these passages refer to a "triplet regimen", this is common terminology used where the 5-FU and LV combination is considered, together, as one part of the three components. See, for example, paragraphs [0026] on page 9 and paragraph [0060] on page 16 of the patent.

had the best Overall Response Rate (ORR), as well as the best Disease Control Rate (DCR) and the highest Progression Free Survival (PFS).

5.17 The patent also discloses the results of a dose exploration human clinical trial in Example 4 (see pages 31 to 33), where certain dosage combinations of the components were trialled for safety and tolerability. The conclusion provided in paragraph [0152] of the patent is that the claimed dosage regimen was **well tolerated in a human clinical trial**.

5.18 Therefore, the patent contains in human data showing that the claimed combination therapy is safe and tolerable, as well as *in vivo* data demonstrating that there was an improvement in efficacy for the claimed drug combination over the FOLFIRINOX regimen from D10.

5.19 Following on from the data in the patent, D18 is a report on the phase I/II study of the "NALIRIFOX" regimen as a first-line treatment of pancreatic adenocarcinoma. The NALIRIFOX regimen is summarised in the "Results" section of the abstract on page 15 of D18. This regimen used the maximum tolerated dose (MTD) which had been ascertained in a dose exploration cohort. This regimen was then taken forward to a dose expansion stage. The regimen is as follows:

Drugs and doses:	liposomal irinotecan – 50 mg/m^2 [free-base equivalent]
	oxaliplatin – 60 mg/m^2
	leucovorin – 400 mg/m^2
	5-fluorouracil – 2,400 mg/m^2
Dosage frequency:	Once every two weeks

5.20 The patent, at paragraph [0009], confirms that a 50 mg/m^2 dose of liposomal irinotecan as the free base, is equivalent to a 60 mg/m^2 dose of liposomal irinotecan as the hydrochloride trihydrate. That is, a 50 mg/m^2 dose of liposomal irinotecan as the free base provides the same amount of irinotecan as that which is provided by a 60 mg/m^2 dose expressed as the equivalent hydrochloride trihydrate dose. Paragraph [0009] also confirms that the doses expressed throughout the patent are expressed in terms of the dose of the hydrochloride trihydrate. Therefore the 50 mg/m^2 dose in D18 expressed in terms of free base equivalent is identical to the dose of liposomal irinotecan in the claims (which, as stated above, is expressed in terms of the amount of hydrochloride trihydrate). The dosage values given for 5-FU, leucovorin, and oxaliplatin in D18 are identical to those in the claims, as well as the dosage frequency (and the patients treated).

5.21 The results of the dose exploration part of the study in D18 (i.e. part 1) correspond to the results in Example 4 of the patent, as discussed above. D18 thus builds on the trial results from Example 4 in the patent by providing efficacy and safety results from part 2 of the clinical trial protocol described in Example 3 in the patent[18].

5.22 Additionally, D18 discusses a comparison of the efficacy of the NALIRIFOX regimen (i.e. the claimed regimen) with the FOLFIRINOX trial regimen in D10 (which is reference 5 in D18), i.e. the closest prior art. The paragraph bridging the columns on page 21 of D18 discusses this

[18] As is made clear, the efficacy and safety results for the pooled population include the dose-expansion cohort, as well as original cohort B from the dose-exploration cohorts, see Figure 1 and its footnote c.

comparison, and the results are summarised in the table below. As the table shows, numerical improvements in both PFS[19] and OS[20], i.e. the secondary efficacy endpoints from the NALIRIFOX trial, are shown in comparison to the FOLFIRINOX trial[21]. An increase of nearly 3 months in progression free survival (with no overlap at all in the 95% confidence interval) is a significant efficacy improvement to the treatment of patients with pancreatic adenocarcinoma, with an increase in mean overall survival of 1.5 months. These improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the closest prior art.

Outcome/endpoint	**NALIRIFOX (D18)**	**FOLFIRINOX (D10)**
Median progression free survival (PFS)[22]	9.2 months (95% CI: 7.69-11.96)	6.4 months (95% CI: 5.5-7.2)
Median overall survival (OS)	12.6 months (95% CI: 8.74-18.69)	11.1 months (95% CI: 9.0-13.1)

5.23 Safety results are also reported in section 3.2.3 of D18 (pages 17 to 20), and summarised in the discussion and conclusions of the paper as having "no unexpected safety outcomes"[23]. In a similar manner to the conclusion in Example 4 of the patent, D18 shows that the claimed dosage regimen was generally manageable for patients, and thus is considered safe enough to continue to a larger Phase 3 trial (see the conclusions in the paragraph bridging pages 21 and 22). Therefore, D18 provides further evidence that the claimed subject matter is associated with an improvement vis-à-vis D10.

5.24 The data in D18 relates to a patient population where 87.5% of patients receiving NALIRIFOX (i.e. the claimed dosage regimen) had metastatic disease at diagnosis. The data in D18 serve to demonstrate that the claimed subject matter is improved over D10.

5.25 This is confirmed by enclosed D19, which is a declaration provided by one of the authors of D18. D19 comprises data from D18 with adjustments made to focus on the 29 metastatic/type IV tumour stage subpopulation who entered the trial, and to remove from the analysis 3 non-

[19] PFS = Progression-Free Survival, and is measured using Kaplan-Meier methodology, as defined in paragraphs [0122] and [0125] of the patent.
[20] OS = Overall Survival, and is the time from randomization to the date of death from any cause, as defined in paragraph [0125] of the patent.
[21] Additionally, an improvement in Overall Response Rate (ORR) was also shown. Table 3 of D18 shows an ORR of 34.4%, and in D10 the confirmed response rate was 31.8%, which is yet another improvement over the closest prior art.
[22] The "Response Evaluation Criteria in Solid Tumours" ("RECIST") criteria, a standardised set of criteria for evaluating efficacy of treatments of cancerous tumours, are different between the two trials: D10 uses v1.0, and D18/D19 use v1.1. RECIST criteria are not specific to pancreatic cancer, and thus must be applicable to all cancers. A summary of the exact changes is outlined in D20, but it is clear from page 229 that these changes are simply clarifications to the original standard. This change has been shown in the literature to make no tangible difference: D21 and D22 provide comparisons of the two versions in assessing tumour responses with D21 noting that the two versions "provided almost perfect agreement" and D22 indicating that the two versions "showed a highly concordant response assessment". Thus, the concordance in D21 and D22 confirms that the present comparison is valid in spite of the fact that slightly different RECIST criteria were used in D10 and D18/D19.
[23] The drug products used have known safety implications and expected adverse events, which are in line with expectations of an efficacious antineoplastic therapy, and confirmed in Example 4, paragraph [0152] of the patent where the claimed therapy was "well tolerated in a human clinical trial".

metastatic patients. This data may be summarised as follows (with the data from both D18 and D10 included for ease of comparison):

Outcome/endpoint	NALIRIFOX (D18)	NALIRIFOX metastatic (D19)	FOLFIRINOX (D10)
Median progression free survival (PFS)	9.2 months (95% CI: 7.69-11.96)	**9.2 months (95% CI: 7.69-11.96)**	6.4 months (95% CI: 5.5-7.2)
Median overall survival (OS)	12.6 months (95% CI: 8.74-18.69)	**12.7 months (95% CI: 8.74-19.12)**	11.1 months (95% CI: 9.0-13.1)

5.26 As discussed in D19, these efficacy data confirm that the subpopulation of the D18 data for metastatic patients only was equally as good as the whole pooled population in D18, supporting the surprising technical effect mentioned above.

5.27 On the basis of the above, the **objective technical problem** is to provide a **more efficacious** treatment of metastatic adenocarcinoma of the pancreas (in patients that have not previously received chemotherapy for this condition), which is also acceptably safe and tolerable.

The solution would not have been obvious

5.28 Starting from the FOLFIRINOX regimen disclosed in D10, the skilled person, attempting to provide a **more efficacious** treatment of metastatic adenocarcinoma of the pancreas that is also acceptably safe and tolerable, would not have arrived at the claimed invention without an inventive step. The use of the specific, claimed **liposomal** irinotecan in the **specified dosage**, as well as the **other specific dosages** that are required by the claim, would not have been obvious for the skilled person seeking to improve efficacy of the FOLFIRINOX treatment for the reasons outlined below.

FOLFIRINOX in the prior art

5.29 Starting from D10 the skilled person may have consulted the available literature relating to the study in D10 about the FOLFIRINOX regimen, such as that in D3 and D11. None of these documents, either in combination or isolation, would have taught the skilled person to use the claimed solution.

5.30 D10 itself confirms that FOLFIRINOX was an effective first-line treatment for patients with metastatic pancreatic adenocarcinoma (see first sentence of "Discussion" section on page 1822 of D10). Based on D10, there is nothing that would have led the skilled person to the claims. There is no mention of, for example, any liposomal irinotecan, and certainly not the specific irinotecan sucrose octasulfate salt liposome injection required by claim 1. This irinotecan sucrose octasulfate salt liposome injection is a different and distinct active ingredient to the non-liposomal irinotecan used in, for example, D10. Therefore, there is nothing at all in D10 which would have led the skilled person to a solution which requires the use of a different and distinct active ingredient to that discussed in D10. In addition, there is no mention of adjusting any of the dosages in D10 towards those required by the claims. Therefore, the claims would not have been obvious in view of D10 alone.

5.31 D3 is a review article discussing progress with the FOLFIRINOX (FFX) regimen since its introduction to clinical practice in 2010 (see Abstract). Key learnings from D3 are that, in spite of accrued experience with the regimen, various questions remain unanswered, and in particular what the effects of the frequent modifications of the regimen are (see Summary section on page 859). The section entitled "Do Modifications to the FFX Regimen Matter?" on pages 855-856 does, as the Opponents allege, mention the breadth in terms of the known modifications to FOLFIRINOX at the time. However, this section does in no way provide concrete positions on ways of modifying the regimen to improve efficacy, and there is no mention whatsoever of using any kind of liposomal irinotecan[24]. On the discussion in D3 of the removal of the 400 mg/m^2 bolus of 5-FU in particular, a loss of efficacy is suggested by the removal of the bolus, i.e. a loss of efficacy was thought to be associated with decreasing the total amount of 5-FU administered from 2,800 mg/m^2 to 2,400 mg/m^2. This by no means teaches the skilled person that lowering the total dose of 5-FU to 2,400 mg/m^2, would improve efficacy[25].

5.32 On the reduction of the dosage of irinotecan, there is absolutely nothing to suggest that such a marked reduction in dose (from 180 mg/m^2 of non-liposomal irinotecan in FOLFIRINOX, to the 60 mg/m^2 liposomal irinotecan as claimed) would result in an increase in efficacy: comparable efficacy is discussed for a small reduction in relative dosage intensity in the Yale study discussed on page 855, right-hand column of D3, but there is no dose difference of anywhere near the magnitude described in the claims, and no indication of this resulting in improvement. Additionally, in this same section, it is reported that Ohio State physicians noticed that a reduction to only 165 mg/m^2 non-liposomal irinotecan was effective and well tolerated, and that a reduction to 135 mg/m^2 was relevant for "frail and elderly patients", in order to be manageably safe. These do not provide a pointer to the dosage of 60 mg/m^2 of the specific liposomal irinotecan in the claims, and they certainly do not provide any suggestion that the use of this dosage would be associated with improved efficacy when used in the dosage regimen of claim 1.

5.33 The Opponents allege that the reduction in doses (of both irinotecan and oxaliplatin, and to some degree 5-FU) would be obvious as a standard approach in combination therapy for reducing toxicity (which of course is not the problem being solved by the skilled person)[26]. However, the first paragraph of "How is Toxicity of FFX Best Managed?" on page 854 of D3 (reproduced below) confirms that this is not so nearly as simple as the Opponents would have the OD believe:

> *"However, some problems engendered by FFX are either idiosyncratic, not dose related, or not manageable with simple dose reduction and may require more innovative strategies..."*

[24] More specifically, there is no mention whatsoever of the specific irinotecan sucrose octasulfate salt liposome injection required by claim 1.
[25] The proprietor of course notes that the conclusions required further clarification, but the proprietor disagrees that any positive conclusion can be drawn as to the possible benefit of decreasing the overall dose of 5-FU (which in D3 is done by removing the 5-FU bolus) in the FOLFIRINOX regimen.
[26] Additionally, the Opponents have simply referred to "reduction" of doses – the claims do not require ranges of dosages, but instead single values. Even if a reduction of dose were to be a standard tactic for reducing toxicity (which the proprietor refutes), the Opponents have failed to accurately quantify exactly what reduction would have been appropriate for each drug.

Thus, D3 would have taught the skilled person at least some of the toxicity issues associated with FOLFIRINOX cannot be alleviated by simply reducing the dosages.

5.34 D11 relates to the PRODIGE 4/ACCORD 11 trial on the FOLFIRINOX regimen, and is a follow-on publication from D10[27]. This paper focusses on changes in quality of life (QoL) measurements when compared to gemcitabine therapy, concluding that the FOLFIRINOX regimen has a significantly reduced QoL impairment. There is no discussion in D11 on adapting the FOLFIRINOX regimen in any way. Nor is there any discussion in D11 on liposomal irinotecan, or any discussion about the efficacy of FOLFIRINOX and how it might be improved. Accordingly, D11 provides no teaching to the skilled person of relevance to solving the objective technical problem.

The skilled person would not have used liposomal irinotecan with any reasonable expectation of providing an improved treatment

5.35 The Opponents have both alleged that it was part of the skilled person's common general knowledge to substitute standard, non-liposomal irinotecan for the specific claimed liposomal version. However, based on the prior art available at the P1 priority date, this is plainly not the case. The prior art did not provide any expectation that this substitution would provide a more efficacious therapy, because:

(i) there is nothing to conclude that liposomal irinotecan would have been more efficacious than standard irinotecan (D2);

(ii) any promising preclinical data did not translate into equivalent success in human patients (D12, D13, and D14), and

(iii) investigations in the prior art on liposomal irinotecan were mostly monotherapies (D2 Arm A, D12 and D14) and/or were investigated as a second-line therapy (D2, D12 and D14).

5.36 O1 relies on D2 to support their allegation that liposomal irinotecan was known to the skilled person to be "not only a suitable substitution to standard irinotecan, especially when administered in combination with 5-fluorouracil and leucovorin, but even a better alternative to it." The proprietor disagrees that this conclusion would have been taken by the skilled person, chiefly because D2 does not provide any comparison of non-liposomal and liposomal irinotecan.

5.37 D2 is a brief abstract discussing the NAPOLI-1 Phase 3 trial which compared the three following trial arms:

A) MM-398 (liposomal irinotecan) at 120 mg/m^2 once every three weeks (q3w);

B) 5-FU at 2000 mg/m^2 and racemic LV at 200 mg/m^2 for four weeks followed by two-week's rest;

C) MM-398 at 80 mg/m^2, 5-FU at 2400 mg/m^2 and racemic LV at 400 mg/m^2 once every two weeks (q2w).

[27] See the first paragraph of the introduction section on page 23. Reference 1 of D11 is D10.

5.38 The trial investigates these arms as a **second-line therapy**, where the patients have metastatic pancreatic adenocarcinoma (mPAC) progressed on or following gemcitabine-based therapy. Conversely, the claimed invention is a **first-line therapy**. Primarily, the results from second-line cancer treatments simply cannot be extended to first-line cancer treatments. At the stage of needing to resort to a second-line treatment, the considerations from an ethical point of view are entirely different to a first-line treatment: care strategies and priorities are entirely different at these two separate stages, and thus so are the expectations in terms of the safety and efficacy of these two treatments. For example, the efficacy of a second-line therapy is tangibly linked with the first-line therapy received previously, and it is very difficult to ascertain the effect of a change between the components in a second-line therapy without considering the effects from the first-line therapy already received. Additionally, it is possible that, following a first-line therapy, the tumour being treated becomes more malignant and difficult to treat, meaning that an active agent with effects in a first-line therapy is by no means necessarily suitable as a second-line therapy[28]. Moreover, by the time that a second-line therapy is employed, patients are likely to be significantly more sick and thus less able to tolerate therapy than those receiving a first-line therapy. On this basis, the treatment design will need to factor different considerations for the tolerability of the therapy, including its dosages and dosage frequencies, thus reducing the ability to accurately draw conclusions between therapies at the different stages.

5.39 The results section of D2 provides little in the way of conclusions, indicating only that, in this second-line treatment, an improvement was shown between arms C and B by the addition of MM-398. As mentioned above, **nothing in D2 actually provides any comparison of non-liposomal irinotecan to liposomal irinotecan**. Therefore, the Opponent's conclusion that D2 would teach the skilled person that liposomal irinotecan would have been better than standard irinotecan for a first-line treatment of metastatic pancreatic cancer simply cannot be followed.

5.40 Additionally, D2 is a study on a combination therapy that does not contain oxaliplatin, and on that basis the relevance of this disclosure to the claims is very limited. Finally, D2 does not indicate what MM-398 is, beyond that it is "a novel encapsulation of irinotecan in a long-circulating liposome", and there is no indication that this is the specific irinotecan sucrose octasulfate salt liposome injection required by claim 1.

5.41 O2 refers to D12, D13, and D14 in support of its arguments that replacing the non-liposomal irinotecan in FOLFIRINOX with liposomal irinotecan would have been obvious. As with D2, the proprietor disagrees that this is the case.

5.42 D12 evaluates MM-398 as a monotherapy in the second-line therapy (i.e. gemcitabine refractory) of metastatic pancreatic cancer patients, showing that it has "moderate" antitumour activity (see Conclusions section on page 920). D12 does not provide any clinical comparison of the efficacy of liposomal irinotecan versus non-liposomal irinotecan. In fact, any discussion of a comparison is in relation to preclinical studies. These studies allegedly show that improved pharmacokinetics and tumour bio-distribution are shown for the liposomal form of irinotecan versus its non-liposomal form (see page 921 of D1), as well as less accumulation in

[28] See, for example, similar reasoning applied in T 108/09, reasons 2.4.6.

the target organs associated with toxic side effects[29]. Increased efficacy and tolerable toxicity is allegedly shown for the liposomal form in Hann et al. (referenced on pages 921 and 924 of D12, and cited as D13). However, the fact that, in practice, (i) only "moderate" antitumour activity was observed in human patients (see Conclusion section on page 920), (ii) it was of only a comparable efficacy (i.e. not improved efficacy) profile to other prior art treatments (see Discussion section on page 924: "its efficacy profile appears similar to that seen with FOLFIRI in the GISCAD trial for the same patient population"), and (iii) it had advantages of being a monotherapy (i.e. entirely different to the claimed combination treatment), all provide evidence that the preclinical data provides no expectation of success in providing a more efficacious therapy in replacing the standard irinotecan with a specific liposomal form.

5.43 O2 alleges that D12 points the skilled person to explore the potential of liposomal irinotecan as a first-line therapy. However, it is evident that the disclosure in the final paragraph of the "Discussion" section on page 924 (see below) goes no way whatsoever toward suggesting that the skilled person would have been led to the claimed dosage regimen as a first-line therapy with a reasonable expectation of success. This passage, instead, would have been considered a vague discussion lacking concreteness, and would have pointed to alternative indications instead of the claimed indication.

> EudraCT Number: 2011-004687-30). Additional studies may explore this drug's potential role in the first-line setting and as part of combination regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

This statement is entirely general[30], discussed not in the context of adjusting FOLFIRINOX. The first sentence of the passage would, if anything, incite the skilled person to investigate the use of liposomal irinotecan as a first-line monotherapy. "[C]ombination regimens" are referred to, albeit in a very general sense with no mention of, for example, possible combination partners or dosages. In the second sentence there is a brief discussion of the FOLFIRINOX regimen. The paper indicates that the prevalence of FOLFIRINOX and its good performance status would, alternatively, have incited the skilled person to instead use liposomal irinotecan in such irinotecan-pretreated patients (i.e. as a second-line therapy to the FOLFIRINOX standard first-line therapy), alone or in combination with gemcitabine. **This document therefore does not teach towards the claimed drug combination or dosage regimen let alone their use as a first-line therapy**.

5.44 D14 offers little beyond what is discussed in D12 (and D13). Foremost, this study was a Phase I study which aimed to define the dose-limiting toxicity and maximum tolerated dose of PEP02[31] as a monotherapy in patients with various different types of cancer – only one of these patients had "pancreatic cancer" (and there is no explicit statement that the pancreatic cancer was metastatic). All patients were treatment-refractory (i.e. they had previously received chemotherapy prior to the trial), unlike the present claims which relate to a first-line

[29] The proprietor notes that no citation is provided to support these particular preclinical studies.
[30] Reference here to "combination regimens" is not contextualised.
[31] PEP02 is MM-398, see D14, first page, left-hand column.

therapy. For these various reasons, any efficacy conclusions drawn from D14 are of scant relevance to a treatment for the specific patient population as claimed, and certainly provide no pointer towards the claimed regimen.

5.45 D14 discusses, on page 580, paragraph bridging the columns, that there were alleged improvements in preclinical studies in pharmacokinetic properties and anti-tumour activity for PEP02. However, there is nothing to suggest that this would translate to improved efficacy in treating the patient population defined in claim 1. In addition, there is no indication what the purported improvement referred to in D14 is relative to. Thus, D14 would not have led the skilled person to the claimed subject matter with a reasonable expectation of successfully solving the objective technical problem in the manner required by claim 1.

5.46 In summary, based on the available prior art at the priority date, there was nothing that would have motivated the skilled person to replace the non-liposomal irinotecan in the FOLFIRINOX with the specific liposomal irinotecan required by claim 1 with any expectation of successfully providing a more efficacious first-line treatment of metastatic pancreatic adenocarcinoma.

The claimed dosages would not have been obvious

5.47 Compared to the FOLFIRINOX treatment in D10, there are further differences to the claimed regimen in the specific dosages: **60 mg/m²** of liposomal irinotecan (D10 uses non-liposomal irinotecan at a **180 mg/m²** dose); **60 mg/m²** oxaliplatin (D10 uses **85 mg/m²** oxaliplatin); and **2,400 mg/m²** 5-fluorouracil (D10 uses **2,800 mg/m² 5-fluorouracil**, by way of a **400 mg/m²** bolus before a **2,400 mg/m²** administration). As will be explained below, the skilled person starting from D10 and faced with the objective technical problem would not have been led to a solution which, *inter alia*, uses these specific doses. In summary, the doses of the components in the claims have unexpectedly been found to provide a more efficacious therapy than in the prior art. There is nothing in the prior art that would have taught or suggested to the skilled person to use these specific dosages with this problem in mind. As will be explained in detail below, there was a high degree of unpredictability in dosages disclosed in the prior art and there was a distinct lack of teaching or pointers towards the claimed solution. This unpredictability and lack of teaching demonstrates that the skilled person would not have been led to the dosages recited in claim 1 with a reasonable expectation of success.

5.48 The Opponents' arguments can be summarised as follows:

- The discovery of the optimum dose for providing a known or obvious therapeutic effect is routine and does not require inventive skill (T 1760/08, T 1409/06).
- For combination therapies, the overall therapeutic benefit is greater than the sum of drugs individually so more favourable outcomes can be achieved at a lower dose with equal or increased efficacy, citing D9, p1045, RHC 2nd para and p1046, RHC 2nd para, and to reduce dose-limiting toxicities, citing T 2506/12.
- The use of lower doses was obvious as they were either taught in the prior art, or were obvious modifications derived from the common general knowledge.

Each of these points will be addressed in turn.

5.49 T 1760/08 and T 1409/06 are cited by the Opponents to support their arguments that discovering an optimum dose for providing a known or obvious therapeutic effect is routine and non-inventive. However, these cases are not relevant here because, as explained above, the claimed invention is not concerned with providing, for example, an optimum dose for providing a known or obvious therapeutic effect. Rather, the claimed invention provides a new, non-obvious, and improved treatment for metastatic pancreatic adenocarcinoma for the patient population defined in claim 1. Therefore, T 1760/08 and T 1409/06 fail to assist the Opponents' case.

5.50 Regarding the expectations of combination therapies, it should be emphasised that, when starting from the closest prior art in D10, the skilled person is already presented with a combination therapy. The skilled person is not starting from the point of a monotherapy, and making adjustments to account for the typical considerations of dosing combination therapies. The discussion in D9, which is a very broad discussion of combination strategies in cancer treatments, is limited to alleged therapeutic benefits comparing the combination therapy with the individual drugs. This is not relevant to the matter in hand, because the skilled person is starting from a known combination therapy. There is nothing in D9 that talks about adjusting known combinations, and certainly there is nothing teaching the skilled person to adjust the specific doses in D10 as per the claims. Likewise, T 2506/12 talks to the alleged benefits of reducing toxicity of the monotherapies through combination therapy. Again, the skilled person is not starting from a monotherapy here, so this not relevant.

5.51 Importantly, the set of facts in T 2506/12 are entirely different to the claims. The discussion in reasons 3.14 of T 2506/12 refers to a claim which was <u>not limited</u> by any dosages of the combination drugs. This discussion therefore is taken entirely out of context by O1, because in T 2506/12 the sole technical difference between claim 1 and the prior art was the fact that the claim required effective treatment of cancer of the human body (see reasons 3.4). Therefore, the skilled person did not need to actually provide <u>specific</u> dosages when solving the technical problem, which in any case was less ambitious than the present technical problem. Regarding the discussion in reasons 4.3, this referred to the auxiliary request I claims, which were limited only by their <u>upper dosage limits</u>. Again, this is an entirely different scenario to the present claims, where specific dosages of each component are required. This case is simply not relevant to the facts of this case, and has been taken out of context by O1 (and endorsed as such by O2).

5.52 A major flaw in Opponents' arguments is that the notable difference in doses between the claims and D10 result in an increase in efficacy as noted above. It would have been entirely contrary to the skilled person's expectation, starting from the D10 FOLFIRINOX, that the <u>reductions</u> in dose referred to above would give such increased efficacy. No case law or document referred to by the Opponents contradicts this.

5.53 Moreover, as mentioned in 5.33 above, D3 already taught the skilled person that at least some of the problems associated with FOLFIRINOX "are either idiosyncratic, not dose related, or not manageable with simple dose reduction and may require more innovative strategies". Therefore in the context of this therapy, the skilled person would have been aware reducing the doses would not necessarily alleviate the problems associated with FOLFIRINOX.

5.54 In relation to the prior art cited and the common general knowledge, there is nothing that would have led the skilled person to make precisely the differences to the FOLFIRINOX regime that claim 1 requires with an expectation of solving the objective technical problem. The teachings of D10, D3 and D11 in this respect have already been discussed above.

5.55 O2 in particular points to D14 which, in combination with the flawed reasoning with reference to T 2506/12, it claims would have led the skilled person to the 60 mg/m^2 dose of liposomal irinotecan. O2's arguments here are flawed for several reasons.

5.56 To treat the various solid tumours in D14, three different monotherapy dosages of PEP02 were given: 60 mg/m^2, 120 mg/m^2 and 180 mg/m^2, and the maximum tolerated dose (MTD) was ascertained as 120 mg/m^2. However, these dosages were administered every 3 weeks whereas the claims require treatment once every two weeks. On this basis, a "dose intensity" can be calculated and compared between D14 and the claims (and the other prior art): the MTD of PEP02 in D14, 120 mg/m^2 over three weeks, has a dose intensity of 40 mg/m^2/week, whereas the claims define a dose intensity of the specified liposomal irinotecan of 30 mg/m^2/week. These are therefore clearly not the same, and this provides a further reason why the D14 would have not led the skilled person towards the claimed subject matter. In any case, the fact remains that the two-week dosage frequency is not disclosed or suggested in D14. This could have had implications on the efficacy and tolerability of the treatment; the skilled person would have understood that it is highly unlikely that administration frequency can simply be adjusted in a linear fashion (e.g. to the point of assuming that dose intensity could be extended to providing enormous doses, at a very low frequency). Finally, the conclusion for the pancreatic cancer patient under efficacy (page 583, paragraph that bridges the columns), noting of course that this is a single patient in a non-efficacy enabled Phase I study, is that a partial response was seen with a 180 mg/m^2 dose (i.e. a 60 mg/m^2/week dose intensity). Inventive skill would have been required for the skilled person to conclude from this result that exactly a 60 mg/m^2 dose once every two weeks (i.e. a 30 mg/m^2/week dose intensity) of liposomal irinotecan according to claim 1, in combination with the other specific drugs at the specific doses given in claim 1, would provide a more efficacious treatment for first-line treatment of metastatic adenocarcinoma of the pancreas. This is because, as stated above, there is no teaching or pointer whatsoever towards this claimed solution in the prior art.

5.57 Moreover, O2's arguments in respect of D14 demonstrate a fundamental inconsistency in their position. O2 argues that, based on D14 (which relates to the treatment of a different patient population to that required by claim 1), the skilled person would have reduced the dose of PEP02 (i.e. liposomal irinotecan) when combining it with additional components. However, this is entirely inconsistent with the fact that in the FOLFIRINOX regimen, e.g. in D10 (which is administered to the same patient population as that required by claim 1), the dosages of non-liposomal irinotecan used in the combination therapy are significantly higher than in D14: in D10, the dosage of irinotecan is 180 mg q2w, i.e. a dose intensity of 90 mg/m^2/week, whereas D14 indicates that the MTD of liposomal irinotecan is far lower, at 120 mg q3w, i.e. a dose intensity of 40 mg/m^2/week. Reducing the dose of PEP02 is also at odds with the discussion in D14 that indicates that PEP02 has a "lower toxicity profile" and thus, if anything, there would have been an expectation that a dose reduction would have been unnecessary (see page 584 of D14, discussed by O2 in (24) of its opposition). Accordingly, the O2's arguments on D14 simply cannot be followed.

5.58 O2 also points to D12 and D15, and alleges that the 60 mg/m^2 liposomal irinotecan (once every 2 weeks) dose as claimed was "within those previously studied", so would be selected without invention. Exactly what is meant by being "within those previously studied" is unclear, and in fact appears to be a tacit acceptance that the specific dose had not actually been previously investigated, pursued, or indeed disclosed anywhere, which of course is the case. What is actually shown in these documents is clear evidence of the unpredictability of dosing liposomal irinotecan in the prior art.

5.59 D15 is an abstract on a Phase I study of PEP02 (MM-398) in combination with high-dose fluorouracil and leucovorin. D15 also does not indicate what PEP02 is, and provides no indication that it is the specific irinotecan sucrose octasulfate salt liposome injection required by claim 1. D15 provides no efficacy conclusions whatsoever, only that the MTD for this specific combination was 80 mg/m^2 of PEP02 given every three weeks, i.e. a dose intensity of ~26.5 mg/m^2/week, which is lower than the dosage intensity of the specific liposomal irinotecan in the claims (30 mg/m^2/week). However, following the logic of O2, the addition of a further component into the combination therapy (i.e. oxaliplatin, as in the claims) would necessitate a yet further reduction in the dose intensity of irinotecan. Had the skilled person done this, as O2 argues, this dose reduction would reduce the dose intensity further, and thus would have taken the skilled person further away from the claimed subject matter.

5.60 In contrast, D2, as discussed above, discloses in arm (C) a q2w (once every two weeks) dose of MM-398 – in combination with the same dosage of 5-FU and LV as in D14 – of 80 mg/m^2, i.e. a dose intensity of 40 mg/m^2/week. D2 provides the results of a successful Phase 3 trial. Therefore, it is clear from the different approaches to dosing liposomal irinotecan, that there was a high degree of unpredictability in the art, and accordingly a low expectation of success for providing an efficacious, let alone more efficacious, treatment using specific dosages.

5.61 D12 describes a monotherapy Phase 2 study into second-line treatment of metastatic pancreatic cancer using PEP02. O2 points to the discussion of the reduction of the starting dose from 120 mg/m^2 to a lower starting dose at 100 mg/m^2. The D12 dosages are all given every 3 weeks, and therefore the 120 mg/m^2 dose corresponds to a 40 mg/m^2/week dose intensity, and the 100 mg/m^2 dose corresponds to a 33.3 mg/m^2/week. None of these dose intensities are the same as the claims. In much the similar way to D12, there is no indication whatsoever that further reduction might be required, such as in the claimed combination therapies, nor to any specific further reduced values. D12 therefore provides no pointer towards the claimed dosage of liposomal irinotecan, nor to the claimed dosage frequency.

5.62 Interestingly, neither opponent is able to point to anything in the prior art relating to the claimed dosage of oxaliplatin. O2 points to an "equal level of preference" in the patent for 60, 75 and 85 mg/m^2, as if to suggest that this is relevant to what the skilled person would have done at the priority date. This is clearly not relevant, because the disclosure of the patent was not part of the state of the art at the priority date. This attempt by O2 to rely on information in the patent when attacking inventive step is indicative of the hindsight analysis which permeates though O2's arguments. Both opponents attempt to diminish the difference in doses between D10 and the claims as insignificant, with O1 calling the dose difference

"small"[32] and O2 calling it "slightly different"[33]. No evidence has been provided by either opponent to support these arguments. However, the proprietor submits that the skilled person would not consider a percentage difference of nearly 35% in the oxaliplatin dosage (i.e. from 85 mg/m^2 to 60 mg/m^2) as being "small", or "slight". With no pointer referred to in the prior art for making this dose reduction, the skilled person simply would not have had any expectation that reducing this dose by this significant amount would have provided a safe and efficacious treatment, let alone a more efficacious treatment than in D10.

5.63 As O2 points out, the patent, in paragraph [0003], indicates that an example of modifying the FOLFIRINOX to account for its toxicity was to eliminate the bolus of 5-FU (such as the bolus that is disclosed in D10), and thus reduce the overall dosage of 5-FU. However, as mentioned above, and as acknowledged in paragraph [0003], this reduction of the overall dosage of 5-FU, at the priority date, had **unknown effects on efficacy and safety**. As discussed above, there are no concrete conclusions in D3 on what the effect is of removing the 5-FU bolus and thus reducing the overall dose of 5-FU from 2,800 mg/m^2 in total (see page 855, paragraph bridging the columns), and certain studies suggest a dose reduction of 400 mg/m^2 (by removing the 5-FU bolus) could lead to loss of efficacy. D3 merely concludes that longer-follow-up will be needed. Referring to D16 (which was also discussed by O2), this abstract merely indicates that, in one study, reducing the dose by removal of the 5-FU bolus "maintained efficacy", i.e. did not improve it. It is also noted that D16 doesn't actually confirm how much 5-FU was dosed as a bolus and thus how much 5-FU was eliminated; it is therefore unclear what the final dose of 5-FU was. Therefore, placed in the context of the later-published review D2, D16 would have offered the skilled person no motivation to remove the bolus of 5-FU in the expectation of providing a more efficacious therapy.

5.64 To the extent that the Opponents wish to continue advancing arguments that reduction of dosages was well known and would have been attempted by the skilled person (which the proprietor of course refuses), both O1 and O2 have failed to provide any indication in the prior art that the exact dosages claimed would have been obvious. The claims do not refer to broad ranges of dosages, but instead to specific values which are not disclosed or suggested anywhere in the prior art.

5.65 In summary, the Opponents' arguments rely on a combination of a large number of prior art references to argue that the differences between the closest prior art and the claims were not obvious. O2 in particular relies on all of D12, D13, D14, D15 and D16. However, O2's arguments cherry pick disclosures from prior art documents and use them to conclude, with hindsight knowledge of the invention, that the claims are obvious. O2 gives no indication or explanation as to why any of these documents are common general knowledge, nor is any actual explanation given as to why it would have been obvious for the skilled person to combine these documents (see T 552/89 with reference to Case Law of the Boards of Appeal I.D.9.7)[34].

5.66 The skilled person would not have concluded that the dosages claimed could provide a more efficacious treatment that is also acceptably safe and tolerable. Rather, the skilled person

[32] O1 statement of opposition, 5.3.11.
[33] O2 statement of opposition, (33).
[34] Of course, as discussed above, O2's assertions about the teaching of the prior are incorrect; of note is that nowhere in the cited prior art is the 60 mg/m^2 dose of oxaliplatin disclosed, let alone taught towards.

would have been motivated instead to retain as high a dosage as is tolerable and safe. This, surprisingly, was not the case for the present treatment, which uses lower doses of the drugs and is more efficacious, and on this basis, the dosage differences between the closest prior art and the claims would not have been obvious.

5.67 Put simply, the inventors of the present patent have found the sweet spot for the dosing of a first-line treatment of metastatic pancreatic adenocarcinoma, made in the absence of any pointers or suggestions in the prior art of how to achieve this, i.e. by the dosage regimen in claim 1.

Conclusion on inventive step

5.68 The patent demonstrates for the first time that irinotecan sucrose octasulfate salt liposome injection, when administered with oxaliplatin, 5-FU, and leucovorin according to claim 1, is able to treat metastatic adenocarcinoma of the pancreas in a first-line setting. In fact, it demonstrates that irinotecan sucrose octasulfate salt liposome injection, when administered according to claim 1, is able to provide more efficacious treatment than the treatment in closest prior art (D10), with acceptable tolerability and side effects.

5.69 The Opponents' arguments on inventive step fail to establish that the skilled person **would** have been led to the claimed subject matter with a reasonable expectation of solving the objective technical problem. At best, they focus on what the skilled person **could** have done.

5.70 Therefore, the claims are inventive, in accordance with Article 56 EPC.

D4, D5, and D7 fail to advance the opponents' case; D1, D6 and D8 are not prior art

5.71 D4, D5, and D7 were all published **after** P1's filing date, and so are not relevant for assessing inventive step. However, O1 argues that D4, D5 and D7, by their nature as the prescribing information for an authorised drug (D4) or as review articles (D5 and D7), are "an account of the common general knowledge and the state of the art prior to their own publication date", or are "evidence of the common general knowledge prior to the effective date of the contested patent". O1 refers to decisions of the Board of Appeal (T 777/08 and T 1641/11) to support this position. However, close inspection of these decisions renders O1's logic severely lacking in relation to the present scenario.

5.72 T 777/08 relies on the publication of the review article as being "in the same month", and as being corroborated by the disclosure of other documents (which were published before the effective date). None of D4, D5 or D7 were published in the same month as P1's priority date (21st August 2015 - D4 was "revised" in October 2015, D5 was published on 21st December 2015, and D7 was published eight months later on 20th May 2016). Further, O1 has not provided any indication that the contents of these documents would have, at the date of filing of P1, been considered common general knowledge by the skilled person (along with associated explanation as to why any relevant documents are not merely isolated publications, but are actually part of the common general knowledge). The publication of a review article cannot simply provide "evidence" of the common general knowledge back over any extended period of time, to suit the arguments that an opponent wishes to make. Therefore, T 777/08 is not supportive of O1's arguments.

5.73 In T 1641/11, the common general knowledge was found to comprise products which were known to the skilled person and even placed on the market already. This is clearly not

comparable for the prior art in question in this case because the product referred to in D4 had not been "placed on the marked" at the P1 priority date.

5.74 Therefore, none of D4, D5 nor D7 is available prior art (nor evidence of the skilled person's common general knowledge) at the P1 priority date.

5.75 Even if the skilled person were to consider any of what is disclosed in D4, D5 or D7 to represent common general knowledge at the P1 priority date (which is not conceded), the claims would still not have been obvious for the following reasons.

5.76 First, O1 states in 3.2.4 (and elsewhere) that the recommended dose of Onivyde® from D4 is 70 mg/m^2. This is misleading, because it is clearly stated in section 14, on page 14 of D4, that "The ONIVYDE dose of 70 mg/m^2 is based on irinotecan free base (equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate)." As mentioned above, the patent indicates that the dosages of liposomal irinotecan are of the hydrochloride trihydrate form[35]. Therefore, any attempt O1 makes to indicate that the dosage disclosed for the approved Onivyde® treatment in D4 is closer to the claims than other prior art dosages fails.

5.77 D4, of course, relates to the approval of Onivyde® as a second line treatment of metastatic adenocarcinoma of the pancreas in a triple combination (i.e. without oxaliplatin). There is absolutely nothing in D4 that would have led the skilled person towards the claimed treatment, because it relates to a treatment at a different stage of the disease, uses a different combination of active ingredients, and at different dosages. Given the approval of Onivyde®, the skilled person arguably would have been motivated by D4 to use the *same* dosage of liposomal irinotecan (80 mg/m^2, based on the hydrochloride trihydrate), because the skilled person would see that this dose had received regulatory approval.

5.78 D5, as noted by O1, is a review paper published after the P1 priority date and provides a summary of the state of the art regarding MM-398, particularly on its "favourable safety". The discussion of efficacy in D5 is limited to what is in the section titled "Clinical efficacy" on pages 459-460. In pancreatic cancer, the discussion is limited to the Phase II monotherapy trial of MM-398 in D12, and the Phase III NAPOLI-1 trial (see for example D2, and foreshadowed in D12). D2 and D12 have been discussed extensively above: neither provides a comparison between MM-398 and non-liposomal irinotecan, neither relates to the same dosage (nor dosage frequency) of the liposomal irinotecan in the claims, neither showed the improvement in efficacy discussed above, and neither relates to first-line treatment of metastatic pancreatic adenocarcinoma. Therefore, when considering efficacy of MM-398, it offers nothing beyond what has already been discussed above. The only comparison made between MM-398 and "standard irinotecan" (i.e. non-liposomal irinotecan) is on the grounds of safety and tolerability, and not efficacy[36].

5.79 O1 focusses on the paragraph bridging pages 462 and 463 of D5, alleging that, due to its optimized pharmacokinetic and safety profile, MM-398 "may be an ideal substitute of standard irinotecan in the first-line FOLFIRINOX regimen". This passage has been reproduced below. As is clear, the passage provides much less of a conclusion than the opponent suggests, and

[35] Paragraph [0009] of the patent.
[36] See the abstract on page 453 of D5.

when read in the context of the other prior art, it would have provided no teaching towards the claims.

> tion. It is also of interest whether the optimized PK and safety profile of MM-398 over standard irinotecan would make it an ideal substitute for irinotecan in the first-line FOLFIRINOX regimen. This might represent a natural exten-

What this passage in fact says is that, based the optimized PK and safety profile, it is of interest whether or not it would make an ideal substitute for non-liposomal irinotecan. As discussed already in relation to D12 and D14 (see 5.42 and 5.45 above), the allegedly favourable PK profile of MM-398 did not necessarily translate into efficacy in the clinic, so in fact this would not necessarily have made it an ideal substitute for non-liposomal irinotecan. These factors, tied with the uncertainty and unpredictability in the prior art (based on the numerous cited documents referred to by the Opponents, and discussed already in detail – see 5.47 and 5.59-5.63 above, for example) on what exact dosage of liposomal irinotecan to use, provides the skilled person with no reasonable expectation of success in making the change from non-liposomal irinotecan to a specific dose of the specific irinotecan sucrose octasulfate salt liposome injection as claimed. The skilled person certainly would not have had any reasonable expectation that a more efficacious therapy could be provided by the claimed specific dose of the irinotecan sucrose octasulfate salt liposome injection. Moreover, no citations are given in support of the above statement in D5, and it appears to be based simply on the opinion of the author of the review[37], meaning that it would have been of limited interest to the skilled person.

5.80 D7 is another review article (again, published after the P1 priority date) that, similarly to D5, discusses the benefits of nanoliposomal formulations of irinotecan. The discussion in D7, particularly on page 3005, left-hand column refers to the same studies as D5 does (Ko et al., D12), and much like D5, offers liposomal irinotecan as an alternative to non-liposomal irinotecan in FOLFIRINOX only because it "*could present* [a] *safe therapeutic option*"[38]. There is no mention of, for example, any possible improvement in efficacy. In fact, the same fundamental differences as in D5 (second-line treatments, no efficacy comparison of liposomal versus non-liposomal irinotecan, different dosages and dosage frequencies, and the preclinical data that did not translate into success in human patients) apply equally to D7.

The claims are nonobvious even if the objective technical problem is formulated less ambitiously

5.81 It has been established above that the claimed subject matter provides a nonobvious solution to the objective technical problem formulated at 5.27 above. However, even if the objective technical problem is formulated less ambitiously as, for example, the provision of a safe and effective treatment for metastatic adenocarcinoma of the pancreas in patients that have not previously received chemotherapy for this condition (which we believe would not be correct), it remains the case that the claimed subject matter is nonobvious. In particular, the cited prior art would not have led the skilled person to use irinotecan sucrose octasulfate salt liposome

[37] The section is titled "Future perspective", and is phrased conditionally so as to make it clear that it is the author's opinion and not an objective, factual summary of the prior art.
[38] D7, page 3005, LH-column under heading "*Onivyde for gemcitabine-refractory metastatic pancreatic cancer*".

injection, oxaliplatin, 5-FU, and leucovorin at the doses given in claim 1 with a reasonable expectation of providing a safe and effective therapy, the above arguments applying *mutatis mutandis*. Therefore, the requirements of Article 56 EPC are met even if the problem is formulated less ambitiously.

Inventive step at the PCT filing date

5.82 Should the OD come to the conclusion that the claims are not entitled to the P1 priority date (which the proprietor disagrees with for the reasons set out in section 4 above), the claims would, in any event, be inventive over the prior art available at the PCT filing date.

FOLFIRINOX (D10) as closest prior art

5.83 O1 proposed, in its alternative arguments, that D3 can be the closest prior art. For the reasons outlined in 5.6 to 5.11 above, D10 represents a more appropriate closest prior art embodiment for the FOLFIRINOX regimen which is discussed in at least D3, D10 and D11.

5.84 The proprietor has already outlined why the claims are inventive when considering D10 as closest prior art, and all of this reasoning applies equally at the PCT filing date. D4, D5 and D7 are discussed in above and, when considered at the filing date, would not render the claims obvious for the same reasons. The only documents not already discussed above are D1, D6 and D8 (all of which were published after the P1 priority date).

5.85 D1 and D6 both relate to a clinical trial protocol. Neither D1 nor D6 provides any guidance to the skilled person on any of the dosage amounts that are to be explored in the trial, nor to the intended dosage frequencies of the components. It is only mentioned that nal-IRI (i.e. liposomal irinotecan, with no mention whether this is the same specific irinotecan sucrose octasulfate salt liposome injection as in claim 1) is to be investigated in one arm in combination with 5-FU/LV and oxaliplatin, and in another arm in combination with only 5-FU/LV. These documents do not contain any disclosure or indication of results or of actual treatment, nor do they hint at any expectations from the trials to be run. Therefore, assuming the skilled person would have considered these as relevant disclosures when trying to provide an improved therapy over FOLFIRINOX (which is not conceded), there would be no relevant teaching towards the specific dosage regimen in the claims. Further, the mere fact that a liposomal irinotecan (and not specifically irinotecan sucrose octasulfate salt liposome injection) was being investigated in this combination in D1 and D6 (instead of non-liposomal irinotecan in FOLFIRINOX) does not provide the skilled person with any reasonable expectation of success of a more efficacious treatment by making this change to FOLFIRINOX.

5.86 D8, which is a qualitative abstract, discusses preclinical data with a comparison between liposomal and non-liposomal irinotecan. There is no data in this abstract to substantiate the conclusions that are discussed. As was the case for, for example, D12, D13, and D14, D8 would not have given the skilled person any motivation to replace the non-liposomal irinotecan in FOLFIRINOX with liposomal irinotecan in the expectation of providing an improved treatment, and certainly not with the specific irinotecan sucrose octasulfate salt liposome injection required by claim 1, which is a different and distinct active ingredient to the non-liposomal irinotecan in FOLFIRINOX. There is also no discussion whatsoever in D8 of appropriate dosages or administration frequencies for clinical study, with only a reference to

NCT02551991 (D1), which of course does not mention any dosages or administration frequencies.

5.87 Thus, even if the OD unexpectedly does not agree that the claims are entitled to the P1 priority date, the claims are still inventive starting from D10.

D1 (or D6) as closest prior art

5.88 The proprietor disagrees that D1 or D6 are an appropriate closest prior art. FOLFIRINOX, as disclosed in D10, D3 and D11, was a significantly further progressed first-line therapy for the treatment of metastatic pancreatic adenocarcinoma having successfully shown efficacy in a Phase III study. D10 would therefore have been considered a more valid springboard to the invention than D1 and D6 which merely outline a protocol, with no indication of clinical efficacy at the filing date[39]. This is the approach taken by the Board of Appeal in T 2154/14, where it was held that a document that disclosed actual treatment, was a more promising springboard than a document with no report of the outcome of the clinical study it describes, and therefore the document disclosing treatment was the closest prior art. FOLFIRINOX uses three identical active components as the claims, but uses non-liposomal irinotecan instead of the specific irinotecan sucrose octasulfate salt liposome injection, and a specific dose for each of these components is disclosed in D10. D1 and D6 also use three of the same components as the claims, and a "liposomal irinotecan" (not specifically irinotecan sucrose octasulfate salt liposome injection), but no doses are provided for any of these components, nor is a dosage frequency provided for any experimental arm. Therefore, more structural modifications are required to arrive at the invention when starting from D1 or D6 than when starting from FOLFIRINOX in D10 (which was the approach taken by the Boards of Appeal in case T 606/89, and discussed in the Case Law of the Boards of Appeal, I.D.3.2). Functionally, claim 1 is limited to require a treatment of metastatic adenocarcinoma of the pancreas (in a patient who has not previously received chemotherapy to treat this disease, i.e. a first-line treatment). A first-line treatment of metastatic adenocarcinoma of the pancreas is disclosed in D10, but of course there is no disclosure of treatment in D1 or D6. Because of this functional similarity, this adds to the reasons why D10 is a more appropriate closest prior art.

5.89 However, regardless of this conclusion, the claimed invention is still inventive at the PCT filing date if the closest prior art is taken to be either D1 or D6. In line with O1's approach, and for the sake of conciseness, D1 will be referred to as the closest prior art document in this section because the disclosures of D1 and D6 are very similar (and any differences are discussed below in any case).

Distinguishing features and technical effects

5.90 D1 discloses two experimental arms, i.e. two embodiments: Arm 1 is directed to nal-IRI (liposomal irinotecan) + 5-FU/LV + oxaliplatin, whereas Arm 2 is directed to nal-IRI + 5-FU/LV. Firstly, there is no indication whatsoever in D1 that either arm is preferred or more likely to succeed.

5.91 Compared to D1, claim 1 requires the actual treatment of metastatic adenocarcinoma of the pancreas. In addition, claim 1 also requires specific dosages of each component in the

[39] See Guidelines for Examination 2021, G-VII-5.1 – it has not been convincingly shown that these documents are equally valid springboards, with reference to T 320/15.

combination therapy and a specific administration frequency of these components. In particular, the full list of **distinguishing features** between Arm 1 in D1 and the claims is as follows[40]:

- The claims use **60 mg/m²** liposomal irinotecan – no dosage of liposomal irinotecan is disclosed in D1.
- The claims use **60 mg/m²** oxaliplatin whereas – no dosage of oxaliplatin is disclosed in D1.
- The claims use **2,400 mg/m²** 5-fluorouracil – no dosage of 5-fluorouracil is disclosed in D1.
- The claims use **200 mg/m²** of the (l)-form of leucovorin or **400 mg/m²** of the (l+d) racemic form of leucovorin – no dosage of leucovorin is disclosed in D1.
- The liposomal irinotecan in claim 1 is **irinotecan sucrose octasulfate salt liposome injection** – there is no indication of the type of liposomal irinotecan in D1.
- The claims require that the combination therapy is administered to the patients **once every two weeks** – no dosing frequency is disclosed in D1.
- The claims define a tolerable, safe and effective **treatment of metastatic adenocarcinoma of the pancreas** – there is no direct and unambiguous disclosure of a tolerable, safe and effective treatment in D1.

5.92 The **technical effect** of these differences is that a tolerable, safe and effective treatment of metastatic adenocarcinoma of the pancreas (in patients that have not previously received chemotherapy for this condition) is provided. This technical effect is described in paragraphs [0015]-[0023] and Example 4 on pages 31-32 of the patent, as well as in the post-published evidence presented in D18 and D19. This tolerable, safe and effective treatment is discussed in detail under inventive step starting from D10 in sections 5.13-5.26 above.

5.93 The **objective technical problem** is therefore to provide a tolerable, safe, and effective treatment of metastatic adenocarcinoma of the pancreas in patients that have not previously received treatment for this condition.

The solution would not have been obvious

5.94 A full discussion of the prior art and the teaching of the various relevant disclosures has already been provided above in relation to non-obviousness at the priority date and PCT filing date starting from D10. Based on the above formulation of the objective technical problem, this does not materially change the fact that there was simply no pointer or suggestion in any of the cited documents towards the claimed dosage regimen. The prior art is deficient on the specific dosages of the particular components (as mentioned above, no prior art with the claimed oxaliplatin dosage has even been suggested at by either opponent), as well as the

[40] O1 attempts to reduce the number distinguishing features by alleging that the dosage of leucovorin, the dosage of 5-fluorouracil, and the dosing frequency of once every two weeks are "standard in the art and certainly not inventive". As will be discussed below under non-obviousness of the solution, this is not correct. Moreover, the problem and solution approach does not account for "standard"-ness when considering the distinguishing features, and therefore it is not correct to dismiss these distinguishing features when formulating the objective technical problem.

dosage frequencies. Countless questions remained open and unanswered in the prior art as to the way to provide effective, safe and tolerable treatments of metastatic adenocarcinoma of the pancreas as a first-line therapy, and neither opponent has been able to satisfy these omissions in the prior art. In the present case, it is not accurate to draw parallels with case law that refers to the performance of a clinical trial providing a reasonable expectation of success in providing an effective treatment because there are significant further differences (detailed above) between D1 and the claims.

5.95 O1's primary argument is that, because D1 discloses a clinical trial protocol, there is a reasonable expectation of providing a successful treatment by carrying out the trial. O1 refers to both T 2506/12 and T 239/16 to support this point. However, there are significant differences between the facts at hand and these two cases. The claims in the present case have all of the additional technical differences outlined above, in addition to the demonstration of a tolerable, safe and effective treatment of metastatic adenocarcinoma of the pancreas.

5.96 Therefore, the Opponent's position is fundamentally incorrect, because the skilled person would not simply be able to run the clinical trial and arrive at the claim (or indeed at any actual therapy), because they do not have any information on, for example, the required doses of any of the component drugs, nor of the dosing frequency. On this point, it should be emphasised that the skilled person is faced with the disclosure of D1 and D6 only at the PCT filing date. Even if it is the case that certain individuals (e.g. the scientists running the clinical trial described in D1) had knowledge of, for example, the dosages and administration frequencies which should be used, this is of no relevance because this information did not form part of the state of the art, and thus would not have been accessible to the skilled person. Even still, the proprietor disagrees that there would have been a reasonable expectation of success for the treatment based on D1. This is because the prior art does not provide any teaching or suggestion towards the specific dosages or dosing frequency used in the claim. In order to ascertain these dosages and dosing frequency, the skilled person would have had to work with the documentary evidence available to them at the filing date. This documentary evidence does not provide even pointers or suggestions at the claimed dosages or dosing frequency, as discussed above. Contrary to O1's assertion, the differences between the dosages in the claims and the prior art are not simply "small differences". O1 has also avoided discussion of the non-obviousness of certain very important technical differences, as will be discussed below.

D1 and D6 do not render the claims obvious

5.97 First, starting from D1, it is almost entirely ignored by O1 that the study was to investigate two different experimental arms, Arms 1 and 2. Arm 2 would have been at least as interesting to the skilled person as Arm 1. In particular, Arm 1 relates to a regimen consisting of liposomal irinotecan and 5-FU/LV, i.e. **without** oxaliplatin. This regimen is similar to the approved second-line treatment, which is the subject of D4. If anything, in the context of D4, Arm 2 (i.e. the oxaliplatin-free arm) may have been attractive to the skilled person because this specific combination of actives has already been approved by the FDA for the same cancer (albeit in the second-line). Further, the skilled person would have been attracted to the fact that Arm 2 of D4 comprises one fewer drug components (in that it does not contain oxaliplatin), as it would have been easier and simpler to administer and dose. The skilled person would also have noted that it may have been safer because of, for example, the reduced likelihood of

drug-drug interactions. This would have affected the skilled person's mindset when attempting to solve the objective technical problem starting from D1. Likewise, D6 discusses the investigation into both arms, and in fact refers to the "previously demonstrated efficacy in the NAPOLI-1 trial"[41] (see "Methods" section on page 3) which also would, if anything, have pointed towards Arm 2 rather than Arm 1.

5.98 O1 refers to D6, suggesting that there would have been an expectation that a dose reduction may have been needed, with reference to the comments in T 2506/12 about dose reductions compared to monotherapies. As the OD will note, D6 refers only to the need to "confirm the target dose of oxaliplatin". Firstly, this does not provide any expectation that any specific reduction of doses will be necessary versus FOLFIRINOX in D10, for example. Additionally, this does not indicate any need to ascertain doses of the other components in the regimen which, as already discussed in detail above, were not taught or suggested at the filing date. As discussed above in 5.55-5.61, the significant reductions of dosages of the irinotecan in D10 compared to the claimed dosage of the specific irinotecan sucrose octasulfate salt liposome injection in claim 1 is entirely unexplained by the Opponents, and the contradictory suggestions in the prior art for an appropriate dosage of a liposomal irinotecan have been ignored. Further, and as already discussed in at least 5.50, the skilled person was not starting from a monotherapy: the prior art discusses other combination therapies comprising, in various combinations, the active ingredients mentioned in the claims. Therefore, the discussed passages of T 2506/12 (reasons 3.14 and 4.3) are not relevant to the present discussion of obviousness, because there is nothing to suggest that there is a need for a reduction in dosage compared to known combination therapies. Moreover, it is pointed out that the dosage of leucovorin in the FOLFIRINOX treatment (i.e. in D10, as well as in D3 and D11) is 400 mg/m^2 (of (l+d) racemic form), i.e. the same as in the claims. Therefore, even if T 2506/12 in combination with D6 were to be considered relevant, O1 has provided no reasoning why, for example, dosages of certain drugs would need to be reduced, but that the dose of leucovorin should be kept the same as it is in the other prior art documents (e.g. D10).

The claimed dosages and dosage frequencies were not obvious

5.99 As mentioned above, O1 dismissed the dose of 5-FU (2,400 mg/m^2) as belonging to the common general knowledge and thus not a technical difference between the claims and D1. The proprietor disagrees with this assertion. As discussed in 5.63 above, the prior art at the filing date did not provide concrete conclusions that lowering the 5-FU dose by 400 mg/m^2 in, for example, D10 was a beneficial thing to do. There were, at the filing date, multiple studies that had investigated alternative dose modifications to the standard 5-FU administration (400 mg/m^2 bolus followed by 2,400 mg/m^2 infusion, so a total 5-FU administration of 2,800 mg/m^2) – see Table 2 of D3. Some of these were investigating a "drop 5-FU bolus" providing a similar total 5-FU dosage to the claimed dosage, some were investigating dropping the 5-FU bolus with a decreased infusion of 2000 mg/m^2 (i.e. a total administration of 2,000 mg/m^2), and some were investigating a decreased 5-FU bolus of 25%. Each of these had varying results from an efficacy and safety perspective. Clearly, therefore, there was no clear pointer or

[41] The NAPOLI-1 trial is discussed in D2 and in D5 (see page 460 and 462), and is the trial underlying the approved second-line treatment disclosed in D4.

suggestion towards the specific 2400 mg/m^2 dose as claimed as O1 alleges[42]. There is certainly no pointer or suggestion that therapeutic efficacy could be maintained if a 2,400 mg/m^2 dose were used.

5.100 Additionally, O1 dismisses the feature requiring administration "once every two weeks" as being "common", and therefore not contributing towards inventive step. The opponent refers to D3 and D10 in support of this allegation. First, O1 has merely asserted that this was common (general knowledge), without any proof as to why this would have been common general knowledge – the proprietor disputes that this would have been the case. The burden of proof thus rests on O1 to demonstrate that this would have been common general knowledge[43]. Moreover, D3 and D10 refer to entirely a different regimen (FOLFIRINOX), which uses much higher doses of irinotecan and oxaliplatin than the claims require for the specified liposomal irinotecan and oxaliplatin[44]. Further, as has already been made clear from the above, various prior art references were investigating a three-week dosage frequency. In particular, D2, D12, D14 and D15, all of which include treatments including liposomal irinotecan (either as a monotherapy or in combination with 5-FU/LV), discuss a three-week, q3w, or 21-day dosage frequency. O1 has not explained why the skilled person would have been led to a two-week dosing frequency notwithstanding these prior art teachings. There is certainly no clear pointer that, starting from D1 which does not discuss any frequency, the dosage once every two weeks would have been an obvious choice, because there were other relevant studies available to the skilled person that would have suggested an entirely different frequency.

5.101 The specific dosages of liposomal irinotecan and oxaliplatin have also been discussed extensively above. In this case, however, there is no reason why the skilled person starting from D1 would not immediately input the dosages of these components from the FOLFIRINOX regimen (in D10, D3 and D11) and start from there. Nevertheless, assuming that the dosages in D10 were considered (noting of course the difference between liposomal irinotecan as claimed, and the non-liposomal irinotecan in D10), there is nothing that would have directed the skilled person towards the specific dosages of liposomal irinotecan and oxaliplatin as claimed. The reasons for this have been detailed above already, in particular in 5.47-5.67 and 5.75-5.80. Notable, of course, is the distinct uncertainty in the prior art on the appropriate way to dose the components, in particular the specific liposomal irinotecan in a way that would be effective in the first-line treatment of metastatic adenocarcinoma of the pancreas. As mentioned already above, the fact that there is absolutely no disclosure in the cited prior art of the 60 mg/m^2 dosage of oxaliplatin is a compelling confirmation of this.

5.102 O1 refers to T 1760/08 and T 1409/06 to support the argument that the skilled person would have routinely discovered the optimum dosages, when in pursuit of a known or obvious therapeutic effect. However, these cases are not relevant in this scenario for the reasons outlined in section 5.49 above. The present therapy is not simply the optimisation of a dose of

[42] As discussed in 5.63, D16 would be taken in the context of the later-published review D2, and would not be considered to carry significant evidential weight of there being common general knowledge to lower the overall dosage of 5-FU (such as by removing the 5-FU bolus).
[43] This is the requirement set out in Case Law of the Boards of Appeal 2019, I.C.2.8.5 for proving something is common general knowledge.
[44] D10: irinotecan = 180 mg/m^2; oxaliplatin = 85 mg/m^2. In the claims: the specific liposomal irinotecan: 60 mg/m^2; oxaliplatin = 60 mg/m^2.

a known drug for a known indication, because this relates to an entirely new therapy, i.e. the first-line treatment of metastatic adenocarcinoma, using an active ingredient, the specific irinotecan sucrose octasulfate salt liposome injection, which had not previously been shown to be safe or effective in this indication. Moreover, for the numerous reasons discussed above, it is important that the prior art landscape is considered in the context of the relevance of this case. As the OD will appreciate, there was no teaching at the filing date as to what specific dosages and dosage frequencies should be investigated in order to provide tolerable, safe and effective treatments of this condition, and there was certainly no pointer towards the claimed doses. These factors cannot be ignored when considering the scant relevance of T 1760/08 and T 1409/06.

T 2506/12 and T 239/16 are not relevant to the case in hand

5.103 The two cases cited by O1, T 2506/12 and T 239/16, to support the allegation that a clinical study disclosure provides a reasonable expectation of successful treatment, is not relevant to this case where significant further distinguishing features, beyond the confirmation of a treatment, exist between the prior art and the claims. With reference to O1's arguments in 5.3.1-5.39 of O1's opposition, it is important to note that these further distinguishing features mean that T 2506/12 and T 239/16 fail to assist the opponents' case.

5.104 The main request claims at issue in T 2506/12 differed from the closest prior art, D2, in **only** the fact that D2, the clinical trial protocol, did not disclose the effective treatment of cancer (see reasons 3.4):

> *"It has been established above that the disclosure of document D2 differs from the subject-matter of claims 1 and 2 of the main request in that D2 does not disclose the effective treatment of cancer of the human body by the envisaged combination therapy."*

Reasons 3.10 and 3.12 of T 2506/12 (referred to by O1 in support of their arguments) refer to these main request claims. Clearly, therefore, this situation is entirely incomparable to the present claims, where the presence of the additional distinguishing features compared to D1 (as set out in 5.91 above) mean that D1 cannot direct the skilled person to the claimed subject matter with a reasonable expectation of success.

5.105 Regarding T 239/16, the same logic applies. Once again, the passages relied on by O1 (reasons 6.5 and 6.6) refer to the main request claims at issue, which differed versus the closest prior art (document (55)) in only the effective treatment of osteoporosis (reasons 6.3):

> *"As can be seen from the discussion under point 5.2 above, the difference between the disclosure of document (55) and the subject-matter of claims 1 and 2 of the main request lies in the failure of document (55) to directly and unambiguously disclose the effective treatment of osteoporosis."*

Therefore, for the exact same reasons, the scenario discussed here in T 239/16 is entirely irrelevant to the present scenario, where additional technically meaningful features exist which distinguish claim 1 from the clinical trial protocol.

5.106 Further, even if D1 were to have given the skilled person a reasonable expectation that some form of therapy using the four named components in the combination in Arm 1 of D1 would have been successful (which the proprietor disputes), the fact remains that there was still

nothing in the prior art pointing towards the claimed dosages and administration frequencies with any reasonable expectation of success. The reasons for this have been outlined extensively above.

Conclusion on inventive step starting from D1 or D6

5.107 In conclusion, the skilled person would not have been directed towards the claimed subject matter when starting from D1. D1 would not have led the skilled person to the claimed subject matter with a reasonable expectation of success, and this would have been the case even if the Board's conclusions in T 2506/12 or T 239/16 are taken into consideration. Had the skilled person considered the prior art relating to FOLFIRINOX, they would have been aware that "the problems engendered by [FOLFIRINOX] are either idiosyncratic, not dose related, or not manageable with simple dose reduction and may require more innovative strategies"[45] and thus, if anything, would have been motivated instead to look at the dosages in approved therapies involving liposomal irinotecan. For example, D4 might be consulted, for the second-line treatment of metastatic pancreatic adenocarcinoma, where no information is provided on an oxaliplatin dose (because it is not part of the D4 approved products), and the dosage of liposomal irinotecan is different to the claims. Alternatively, the approved FOLFIRINOX regimen may be consulted (e.g. in D10), where different dosages of non-liposomal irinotecan are used, as well as different doses of oxaliplatin, and there was not a confirmed approach to dosing of 5-FU appropriately at the filing date.

5.108 In view of the above, when starting from D1 (or D6) as closest prior art, which the proprietor refutes is the correct approach, the claims are still inventive.

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6 AUXILIARY REQUESTS

6.1 The proprietor considers the claims of the main request allowable for the reasons given above. However, should the OD unexpectedly disagree, the enclosed auxiliary requests are filed to address the opponents' various assertions of lack of priority entitlement, and lack of inventive step.

Auxiliary Request 1

6.2 Auxiliary Request 1 (AR1) is filed in response to the allegations of lack of priority entitlement, and lack of inventive step on this basis.

Article 123(2) EPC

6.3 In addition to the amendments for the Main Request, claims 1, 6, and 9 are amended to specify that the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil. Basis for including this preferred feature into claim 1 is found in the application as filed on page 25, lines 25-26.

Article 76(1) EPC

6.4 This amendment merely confirms priority entitlement to P1, and this wording now matches that of claim 22 of P1 in respect of the administration. When considering priority entitlement to

[45] D3, page 854.

P1 starting from claim 1 of P1, basis for the additional feature is found in at least paragraph [0069] on page 13 of P1.

Article 56 EPC

6.5 For the same reasons as the claims of the Main Request, the claims of AR1 are inventive.

Auxiliary Request 2

6.6 Auxiliary Request 2 (AR2) is filed to strengthen the proprietor's position even further on priority entitlement, and therefore improve the position on inventive step on this basis.

Articles 123(2) and 76(1) EPC

6.7 In addition to the amendments for the Main Request, all dependent claims as granted are deleted.

Article 56 EPC

6.8 For the same reasons as the claims of the Main Request, the claims of AR2 are inventive.

Auxiliary Request 3

6.9 Auxiliary Request 3 (AR3) is a combination of the Main Request, AR1 and AR2, and is therefore allowable for the same reasons.

Main Request – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

2. The liposomal irinotecan for use of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

3. The liposomal irinotecan for use of any one of claims 1-2, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

4. The liposomal irinotecan for use of any one of claims 1-3, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

5. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

6. The liposomal irinotecan for use of any one of claims 1-5, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

7. The liposomal irinotecan for use of any one of claims 1-6, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

8. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil;

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

9. The liposomal irinotecan for use of any one of claims 1-8, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

10. The liposomal irinotecan for use of any one of claims 4, or 5, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.

Main Request – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~2. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate 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).~~

~~32~~. The liposomal irinotecan for use of ~~any one of~~ claim~~s~~ 1-~~2~~, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

~~43~~. The liposomal irinotecan for use of any one of claims 1-~~32~~, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

~~54~~. The liposomal irinotecan for use of any one of claims 1-~~34~~, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

~~65~~. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~76~~. The liposomal irinotecan for use of any one of claims 1-~~56~~, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

~~87~~. The liposomal irinotecan for use of any one of claims 1-~~67~~, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

~~98~~. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~109~~. The liposomal irinotecan for use of any one of claims 1-~~98~~, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

~~11. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan, oxaliplatin and leucovorin are 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, and wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.~~

~~12~~10. The liposomal irinotecan for use of any one of claims ~~5~~4, or ~~5~~6, ~~or 11~~, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.

~~13. The liposomal irinotecan for use of any one of claims 1 or 3-12, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.~~

~~14. The liposomal irinotecan for use of any one of claims 1 or 3-13, 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).~~

Auxiliary request 1 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

2. The liposomal irinotecan for use of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

3. The liposomal irinotecan for use of any one of claims 1-2, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

4. The liposomal irinotecan for use of any one of claims 1-3, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

5. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

6. The liposomal irinotecan for use of any one of claims 1-5, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

7. The liposomal irinotecan for use of any one of claims 1-6, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

8. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil;

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

9. The liposomal irinotecan for use of any one of claims 1-8, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

10. The liposomal irinotecan for use of any one of claims 4, or 5, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.

Auxiliary request 1 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~2. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate 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).~~

~~32~~. The liposomal irinotecan for use of ~~any one of~~ claim~~s~~ 1-~~2~~, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

~~43~~. The liposomal irinotecan for use of any one of claims 1-~~32~~, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

~~54~~. The liposomal irinotecan for use of any one of claims 1-~~34~~, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

~~65~~. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~76~~. The liposomal irinotecan for use of any one of claims 1-~~56~~, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

~~87~~. The liposomal irinotecan for use of any one of claims 1-~~67~~, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

~~98~~. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~109~~. The liposomal irinotecan for use of any one of claims 1-~~98~~, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

~~11. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan, oxaliplatin and leucovorin are 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, and wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.~~

~~12~~10. The liposomal irinotecan for use of any one of claims ~~5~~4, or ~~5~~6, ~~or 11~~, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.

~~13. The liposomal irinotecan for use of any one of claims 1 or 3-12, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.~~

~~14. The liposomal irinotecan for use of any one of claims 1 or 3-13, 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).~~

Auxiliary Request 2 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

Auxiliary Request 2 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~2. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate 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).~~

3. The liposomal irinotecan for use of any one of claims 1-2, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

4. The liposomal irinotecan for use of any one of claims 1-3, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

5. The liposomal irinotecan for use of any one of claims 1-4, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

6. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

7. The liposomal irinotecan for use of any one of claims 1-6, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

8. The liposomal irinotecan for use of any one of claims 1-7, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

9. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the

metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. The liposomal irinotecan for 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.

11. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan, oxaliplatin and leucovorin are 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, and wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

~~12. The liposomal irinotecan for use of any one of claims 5, 6, or 11, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.~~

~~13. The liposomal irinotecan for use of any one of claims 1 or 3-12, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.~~

~~14. The liposomal irinotecan for use of any one of claims 1 or 3-13, 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).~~

Auxiliary Request 3 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

Auxiliary Request 3 – December 2021

Claims:

1. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered intravenously in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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;

    wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

~~2. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,~~

~~wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate 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).~~

3. The liposomal irinotecan for use of any one of claims 1-2, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

4. The liposomal irinotecan for use of any one of claims 1-3, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

5. The liposomal irinotecan for use of any one of claims 1-4, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

6. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

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

7. The liposomal irinotecan for use of any one of claims 1-6, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.

8. The liposomal irinotecan for use of any one of claims 1-7, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

9. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the

metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. The liposomal irinotecan for 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.

11. Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method 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 the (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,

wherein the liposomal irinotecan, oxaliplatin and leucovorin are 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, and wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

~~12. The liposomal irinotecan for use of any one of claims 5, 6, or 11, wherein the administration of the 5-fluorouracil is initiated on days 1 and 15 of a 28-day treatment cycle.~~

~~13. The liposomal irinotecan for use of any one of claims 1 or 3-12, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.~~

~~14. The liposomal irinotecan for use of any one of claims 1 or 3-13, 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).~~

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Original Research

First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study☆,☆☆

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KEYWORDS
Liposomal irinotecan;
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Abstract ***Background:*** This open-label, phase I/II study evaluated safety and efficacy for first-line liposomal irinotecan + oxaliplatin + 5-fluorouracil + leucovorin (NALIRIFOX). ***Methods:*** Patients (aged ≥18 years) had locally advanced/metastatic pancreatic ductal adenocarcinoma (mPDAC), with an Eastern Cooperative Oncology Group performance status score

☆ Prior presentation: The contents of this article satisfy the criteria for originality. Results from this final data cutoff have been presented at: the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2020 – Virtual, 1–4 July, 2020; and the European Society for Medical Oncology Virtual Congress 2020, 19–21 September 2020.

☆☆ Results from earlier data cutoff dates were presented at: the American Association for Cancer Research Special Conference on Pancreatic Cancer: Advances in Science and Clinical Care, 2019, Boston, MA, 6–9 September, 2019; the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2019, Barcelona, Spain, 3–6 July, 2019; and the American Society of Clinical Oncology Annual Conference, Chicago, IL, 1–5 June, 2018.

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[1] At the time the study was conducted.

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'Irinotecan');
Locally advanced pancreatic adenocarcinoma;
Metastatic pancreatic adenocarcinoma (MeSH: 'pancreatic neoplasms', 'carcinoma, pancreatic ductal', 'neoplasm metastasis');
Clinical trial (MeSH: 'clinical trials as topic')

of 0/1 and adequate organ function. Primary objectives were to determine the maximum tolerated dose (MTD) and to evaluate safety and tolerability. Treatment-emergent adverse events (TEAEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Efficacy end-points included progression-free survival (PFS) and overall survival (OS); disease assessments used Response Evaluation Criteria in Solid Tumors 1.1.
Results: The MTD (liposomal irinotecan 50 mg/m^2 [free-base equivalent], oxaliplatin 60 mg/m^2, 5-fluorouracil 2400 mg/m^2, leucovorin 400 mg/m^2 every 2 weeks) was based on dose-limiting toxicities and cumulative safety data in four dose-exploration cohorts. The MTD was received by 32 of 56 patients, seven during dose exploration and 25 during dose expansion (median age 58.0 years [range, 39–76], 28 [87.5%] with metastatic disease at diagnosis [29 at study entry], and one receiving study treatment at data cutoff [26 February 2020]). Of these patients, 22 of 32 had grade ≥3 treatment-related TEAEs, most commonly neutropenia (31.3%), febrile neutropenia (12.5%) and hypokalaemia (12.5%); ten had serious treatment-related TEAEs; and three died from TEAEs considered unrelated to treatment. Median PFS and OS were 9.2 (95% CI: 7.69–11.96) and 12.6 (8.74–18.69) months, respectively.
Conclusion: First-line NALIRIFOX for patients with locally advanced/mPDAC was generally manageable and tolerable. A randomised, controlled phase III study is underway.

1. Introduction

Advanced pancreatic cancer is associated with poor clinical outcomes [1]. Preferred first-line treatment options for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) include gemcitabine + albumin-bound paclitaxel (gemcitabine/nab-paclitaxel) and non-liposomal irinotecan + oxaliplatin + 5-fluorouracil/leucovorin (5-FU/LV) (FOLFIRINOX) [2,3]. Although both regimens provided significant improvements in survival outcomes compared with gemcitabine monotherapy in clinical trials [4,5], survival rates for pancreatic cancer have remained low [6–8]. The research imperative for the treatment of patients with mPDAC therefore remains developing and testing new agents and new combinations in the first-line setting.

The non-liposomal formulation of the topoisomerase I inhibitor irinotecan is a well-established component of various combination therapies [9], including FOLFIRINOX in mPDAC [2,10,11]. However, preclinical and clinical data suggest there may be additional benefits if liposomal irinotecan (ONIVYDE®; historically nal-IRI; Ipsen Biopharmaceuticals, Inc., Cambridge, MA, USA) is substituted for the non-liposomal formulation. Liposomal irinotecan (70 mg/m^2 free-base equivalent), in combination with 5-FU (2400 mg/m^2) and LV (400 mg/m^2), is already a recommended treatment option for patients with mPDAC following progression with gemcitabine-based therapy, based on the results of the NAPOLI-1 phase III trial [2,3,12]. Preclinically, the active metabolite, SN-38, persists longer in tumours after administration of liposomal irinotecan (up to 168 h) than after administration of non-liposomal irinotecan (<48 h) [13]. Furthermore, in patients with mPDAC receiving liposomal irinotecan + 5-FU/LV during NAPOLI-1 [12], longer exposures to unencapsulated SN-38 above a key threshold and higher average plasma concentrations of total irinotecan, total SN-38 and unencapsulated SN-38 were all associated with better overall survival (OS) and progression-free survival (PFS) [14]. Improved anti-tumour activity has also been observed with liposomal versus non-liposomal irinotecan, when administered with oxaliplatin + 5-FU, in a patient-derived xenograft model [15].

This open-label, phase I/II study used the NALIRIFOX regimen, in which liposomal irinotecan replaced the non-liposomal irinotecan component of FOLFIRINOX. It was designed to establish a recommended dose for further study, and to investigate safety/tolerability, efficacy and pharmacokinetics (PK) in patients with locally advanced or mPDAC who had not been treated previously in the advanced/metastatic setting.

2. Methods

2.1. Patients

The study comprised two parts: dose exploration followed by dose expansion. Eligible patients were ≥18 years of age, had histologically or cytologically confirmed pancreatic adenocarcinoma that was locally advanced or metastatic, and had not been treated previously in the advanced/metastatic setting. Patients also had measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [16]; adequate haematological, hepatic and renal function; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 [17] (dose-exploration part) or a Karnofsky Performance Status score of ≥70 [18] (dose-expansion part). Exclusion criteria included

any second malignancy in the previous 3 years and use of strong CYP3A4 inhibitors or inducers, or strong UGT1A1 inhibitors.

2.2. Study design and treatment

This open-label, two-part, phase I/II study enrolled patients between 26 October 2015 and 29 October 2018. The study was conducted at 21 sites in Australia, Spain and the USA. The data cutoff for the long-term follow-up results presented here was 26 February 2020.

Patients received study treatment every 2 weeks (days 1 and 15 of each 28-day cycle). Intravenous treatment was administered sequentially beginning with liposomal irinotecan, then oxaliplatin, LV 400 mg/m^2 and 5-FU 2400 mg/m^2 (no bolus; continuous infusion over 46 h); see Appendix for further details. Patients were intended to receive study treatment until radiologically determined progressive disease (PD) or unacceptable toxicity related to study treatment. Patients could discontinue oxaliplatin alone at the investigator's discretion; otherwise, discontinuation was of all four study drugs. Granulocyte colony stimulating factors (G-CSF) were permitted at investigator discretion, to manage neutropenia or as prophylaxis if patients were considered high risk (see Appendix). Oxaliplatin dose reductions were permitted for sensory neuropathy (see protocol). Survival data and information about subsequent mPDAC therapies were obtained every 8 weeks after discontinuation until death or study completion.

Dose exploration used a traditional 3 + 3 design (see Appendix); with dosing based on that administered in the NAPOLI-1 (liposomal irinotecan 70 mg/m^2 free-base equivalent) and PRODIGE 4 (FOLFIRINOX; oxaliplatin 85 mg/m^2) pivotal studies [5,12]. Doses (in order of testing) were cohort A: liposomal irinotecan 70 mg/m^2 free-base equivalent + oxaliplatin 60 mg/m^2 (70/60); cohort B: 50/60; cohort C: 50/85 (all predetermined); and cohort D: 55/70 (introduced in a protocol amendment, see Appendix). Dose-limiting toxicities (DLTs, defined in Appendix) were measured during cycle 1 (28-day DLT period). Progression to the next cohort occurred after safety evaluation was complete for the last patient enrolled in a cohort.

During dose expansion, patients received the maximum tolerated dose (MTD); those withdrawing were not replaced.

2.3. Assessments and end-points

For dose exploration, the primary objectives were to characterise DLTs and determine the recommended dose. Overall, the primary study objectives were safety and tolerability, with secondary objectives of efficacy and PK.

Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Key TEAEs were defined in the clinical study report (CSR) using MedDRA terms, based on monitoring and the known safety profiles of liposomal irinotecan and oxaliplatin: diarrhoea (grade $\geq$3), febrile neutropenia (any grade), neutropenic sepsis (any grade), neutropenia (grade $\geq$3), thrombo-embolic events (any grade), peripheral neuropathy (grade $\geq$3).

Computerised tomography or magnetic resonance imaging was performed at screening (baseline), every 8 weeks thereafter until radiologically determined PD, and at end of treatment. Disease was evaluated by investigators using RECIST version 1.1. Efficacy end-points included PFS, OS, overall response rate (ORR), the disease control rate at 16 weeks (DCR_{16}) and the duration of response (DoR).

PK analyses and exploratory analyses of survival in *post hoc* subgroups are described in the Appendix.

2.4. Statistical analyses

The sample size for dose exploration was dependent on the number of patients enrolled into cohorts and the toxicity rate. The recommended dose was to be received by at least 30 patients; there was no efficacy hypothesis.

The median PFS and OS were calculated using the Kaplan–Meier method (with hazard ratios [HRs] determined using Cox regression for biomarker subgroups); 95% confidence intervals (CIs) were calculated using Brookmeyer–Crowley methods. For measures of clinical response, patients without a postbaseline tumour assessment were classified as not evaluable. DoR was analysed using the Kaplan–Meier method and 95% CIs were calculated using the Clopper–Pearson and Brookmeyer–Crowley methods for ORR and DCR_{16}, respectively.

Analyses were conducted for the safety and PK populations. Statistical analyses were performed with SAS® software version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA). Censoring rules (Table A1) and population definitions are provided in the Appendix.

2.5. Study oversight

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. Study documentation was approved by an independent ethics committee and institutional review board. Patients provided written informed consent at screening. Protocol amendments made after the study started are described in the protocol.

3. Results

3.1. Dose exploration

Of the 31 patients enrolled for dose exploration, five experienced ≥1 DLT. The doses used in cohorts A and C were not considered tolerable because two patients in each cohort experienced ≥1 DLT. In cohort A (70/60, seven patients), neutropenic infection (grade 4) was reported in one patient and neutropenic sepsis (grade 4) in another patient. In cohort C (50/85, 10 patients), diarrhoea and vomiting were reported in one patient (both grade 4 and > 3 days in duration); and diarrhoea (grade 3, >3 days in duration), anal fissure, anal inflammation and proctalgia (all grade 2 and delayed the next scheduled dose by >14 days) were reported in another patient. Although no patients had DLTs in cohort D (55/70, seven patients), the dose was not considered tolerable following review of grade ≥3 TEAEs. Finally, one patient had a DLT of febrile neutropenia (grade 3) in cohort B (50/60, seven patients). Following review of cumulative safety in this cohort, 50/60 was the MTD recommended for expansion (Fig. 1).

3.2. Population receiving the recommended dose

3.2.1. Patient disposition and baseline characteristics

In total, 32 of the 56 patients enrolled in the study received the recommended dose, seven during dose exploration and 25 during dose expansion (Fig. 1). These patients had a median age of 58.0 years; 87.5% had metastatic disease at diagnosis, 43.8% had liver metastases and 56.3% had an ECOG performance status score of 1 (Table 1).

3.2.2. Treatment

Treatment durations and cumulative doses are reported in Table 2. In total, 31 of 32 patients receiving the recommended dose discontinued study treatment, most commonly because of PD (14 patients) (Fig. 1, Table A2). Of those who discontinued treatment, 25 subsequently received second-line therapy, most commonly gemcitabine/nab-paclitaxel (15 patients) (Appendix).

3.2.3. Safety and tolerability

All 32 patients receiving the recommended dose experienced ≥1 TEAE considered related to treatment (Table

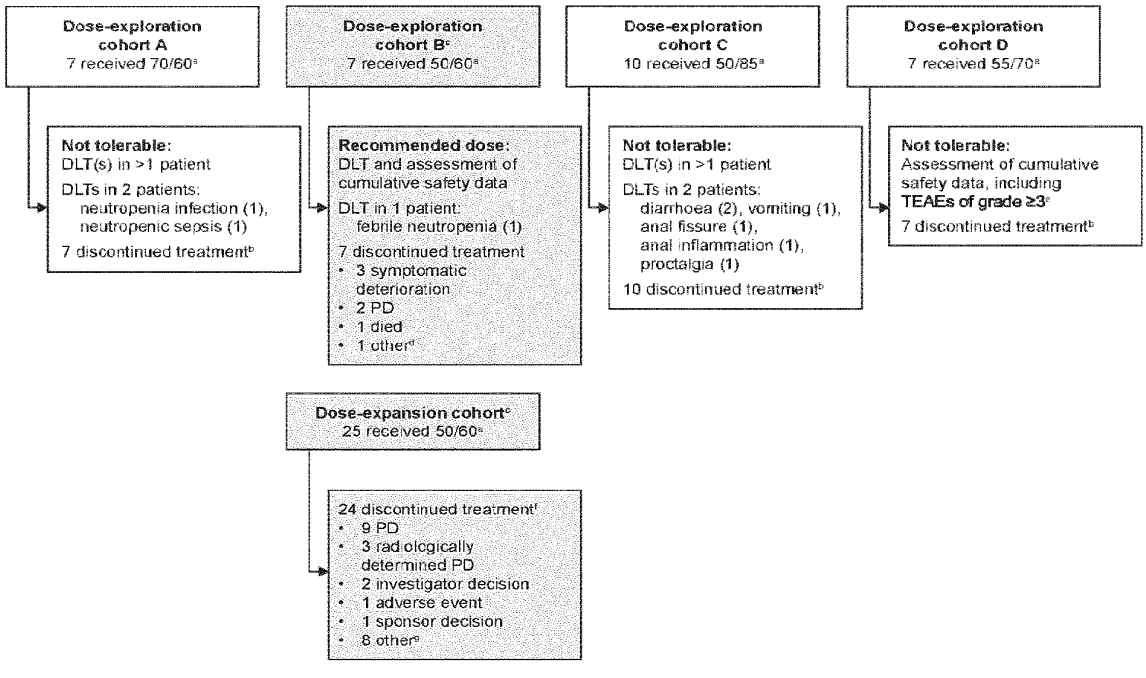

Fig. 1. Flow of patients through the study. [a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 on days 1 and 15 of each 28-day cycle. [b] Reasons for discontinuation are provided in Table A2. [c] Cohorts receiving the recommended dose were included in the pooled population 50/60 for the analysis of efficacy and safety. [d] Owing to patient decision. [e] All TEAEs of grade ≥3 are provided in Table A3. [f] One patient was still receiving treatment at the data cutoff. [g] Owing to patient decision (four patients), clinical progression (two patients), consent withdrawn (one patient) and lack of clinical benefit/adverse event (one patient). [h] All patients in the enrolled population (completed screening successfully with documented enrolment date) were included in the safety and PK populations. Abbreviations: DLT, dose-limiting toxicity; PD, progressive disease; PK, pharmacokinetic.

Table 1
Demographic and disease characteristics at baseline.

Characteristic	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Age, years						
Mean (SD)	66.7 (7.87)	60.4 (10.66)	65.5 (5.21)	63.1 (7.17)	56.8 (9.95)	57.6 (10.05)
Median (range)	64.0 (58–78)	57.0 (44–74)	66.5 (57–73)	61.0 (54–73)	58.0 (39–76)	58.0 (39–76)
Women, No. (%)	6 (85.7)	4 (57.1)	2 (20.0)	2 (28.6)	14 (56.0)	18 (56.3)
Race, No. (%)						
White	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Black or African American	0	0	0	0	2 (8.0)	2 (6.3)
Asian	1 (14.3)	0	1 (10.0)	0	1 (4.0)	1 (3.1)
Missing	0	0	0	0	1 (4.0)	1 (3.1)
ECOG performance status score, No. (%)						
0	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
1	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)
*UGT1A1*28* allele status, No. (%)						
Negative	4 (57.1)	3 (42.9)	5 (50.0)	3 (42.9)	11 (44.0)[c]	14 (43.8)[c]
Homozygous (7/7)	1 (14.3)	1 (14.3)	1 (10.0)	0	1 (4.0)	2 (6.3)
Heterozygous (7/6)	2 (28.6)	2 (28.6)	3 (30.0)	4 (57.1)	11 (44.0)	13 (40.6)
Missing	0	1 (14.3)	1 (10.0)	0	1 (4.0)	2 (6.3)
Tumour stage at diagnosis, No. (%)[d]						
IIA	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
Tumour location, No. (%)						
Head	5 (71.4)	4 (57.1)	3 (30.0)	2 (28.6)	6 (24.0)	10 (31.3)
Body	0	2 (28.6)	6 (60.0)	3 (42.9)	2 (8.0)	4 (12.5)
Tail	1 (14.3)	1 (14.3)	0	1 (14.3)	8 (32.0)	9 (28.1)
Head and body	0	0	0	0	1 (4.0)	1 (3.1)
Body and tail	0	0	1 (10.0)	1 (14.3)	4 (16.0)	4 (12.5)
Missing	1 (14.3)	0	0	0	4 (16.0)	4 (12.5)
Metastatic lesion locations, No. (%)						
Liver	3 (42.9)	2 (28.6)	4 (40.0)	3 (42.9)	12 (48.0)	14 (43.8)
Lung	0	1 (14.3)	2 (20.0)	4 (57.1)	3 (12.0)	4 (12.5)
Lymph nodes	0	0	0	0	1 (4.0)	1 (3.1)
Other	2 (28.6)	4 (57.1)	4 (40.0)	1 (14.3)	16 (64.0)	20 (62.5)
Missing	4 (57.1)	1 (14.3)	4 (40.0)	3 (42.9)	4 (16.0)	5 (15.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 every on days 1 and 15 of each 28-day cycle.
[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.
[c] Excludes one patient with compound heterozygosity for the TA5 and TA7 polymorphisms.
[d] One patient in the dose-expansion cohort received a diagnosis of stage IIA disease but entered the study with stage IV disease.

2). Key TEAEs defined in the CSR (using MedDRA v20.1) were experienced by 19 patients: grade ≥3 neutropenia (10 patients, all considered treatment-related); febrile neutropenia (four patients, all grade ≥3 and considered treatment-related); grade ≥3 diarrhoea (four patients, considered treatment-related in three); thrombo-embolic events (five patients); no patients experienced neutropenic sepsis or grade ≥3 peripheral neuropathy (which was present only in cohort C [50/85, one patient]; Table A3).

The most common grade ≥3 TEAEs apart from neutropenia, febrile neutropenia and diarrhoea (see above) were hypokalaemia (six patients), neutrophil count decreased and alanine aminotransferase increased (four patients each) (Table 2, Table A3).

Grade ≥3 treatment-related TEAEs occurred in 22 of 32 patients; the most common apart from neutropenia, febrile neutropenia and diarrhoea (see above) were hypokalaemia (four patients), nausea (three patients) and neutrophil count decreased (3 patients) (Table A4). The following grade ≥3 treatment-related liver function abnormalities were reported: increases in alanine aminotransferase (two patients), gamma-glutamyltransferase (two patients), aspartate aminotransferase (one patient) and blood alkaline phosphatase (one patient); and hepatotoxicity (one patient).

Table 2
Duration of treatment, cumulative doses and overview of TEAEs.

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Duration of treatment in weeks,[c] mean (SD)						
Liposomal irinotecan	3.8 (5.02)	44.6 (49.26)	23.2 (31.62)	14.0 (16.20)	28.4 (20.36)	31.9 (28.93)
Oxaliplatin	3.8 (5.02)	44.6 (49.26)	15.1 (17.67)	14.0 (16.20)	25.8 (18.61)	29.9 (28.28)
5-Fluorouracil	4.1 (5.02)	44.9 (49.30)	23.5 (31.62)	14.3 (16.20)	28.7 (20.36)	32.2 (28.94)
Leucovorin	3.8 (5.02)	44.6 (49.26)	23.2 (31.62)	14.0 (16.20)	28.4 (20.36)	31.9 (28.94)
Cumulative doses in mg, median (range)						
Liposomal irinotecan	160.5 (79.1 −398.1)	620.5 (59.7 −3574.1)	185.8 (59.8 −2748.2)	326.5 (64.7 −794.3)	632.0 (58.8 −1683.2)	626.2 (58.8 −3574.1)
Oxaliplatin	120.3 (59.4 −359.6)	705.8 (59.7 −3087.7)	269.8 (84.8 −1636.5)	353.3 (69.7 −1221.1)	596.3 (58.8 −1440.4)	598.8 (58.8 −3087.7)
5-Fluorouracil	4813.7 (2373.9 −14444.4)	22844.1 (2400.0 −143350.5)	7867.6 (2400.0 −108238.0)	12081.1 (2388.1 −41865.3)	25347.4 (2352.9 −67326.2)	24862.7 (2352.9 −143350.5)
Leucovorin	802.3 (395.7 −2407.4)	4805.8 (400.0 −23926.0)	1406.8 (400.0 −17966.3)	2012.5 (394.2 −9170.1)	4953.8 (411.8 −12411.1)	4879.8 (400.0 −23926.0)
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Any treatment-related[d] TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Grade ≥3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Any TEAE leading to dose discontinuation[e]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Any TEAE leading to dose adjustment[f]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	6 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death[g]	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)
Treatment-related[d]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)
TEAE of grade ≥3 occurring in ≥5% of the pooled population						
Neutropenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Hypokalaemia	3 (42.9)	2 (28.6)	2 (20.0)	3 (42.9)	4 (16.0)	6 (18.8)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	3 (12.0)	4 (12.5)
Neutrophil count decreased	1 (14.3)	0	1 (10.0)	0	4 (16.0)	4 (12.5)
Febrile neutropenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Alanine aminotransferase increased	0	0	0	0	4 (16.0)	4 (12.5)
Vomiting	1 (14.3)	0	3 (30.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	2 (8.0)	3 (9.4)
Nausea	0	0	3 (30.0)	0	3 (12.0)	3 (9.4)
Abdominal pain	0	0	0	1 (14.3)	3 (12.0)	3 (9.4)
Lymphocyte count decreased	0	0	0	0	3 (12.0)	3 (9.4)
Hypoalbuminemia	1 (14.3)	0	0	0	2 (8.0)	2 (6.3)
Back pain	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Dyspnoea	0	0	0	0	2 (8.0)	2 (6.3)
Gamma-glutamyltransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Hyperglycaemia	0	0	0	0	2 (8.0)	2 (6.3)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

Data are no. (%) of patients from the safety population unless stated otherwise. Events were coded in accordance with the preferred terms in the Medical Dictionary for Regulatory Activities version 20.1 and toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse event.

[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 on days 1 and 15 of each 28-day cycle.

[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.

[c] Duration of treatment (in days) was calculated as (date of last exposure − date of first exposure) + 1, before being converted to weeks.

[d] Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing.

[e] Refers to discontinuation of oxaliplatin alone or all four treatments administered, as described in the protocol. In the PP 50/50, TEAEs leading to discontinuation were peripheral neuropathy (two patients); abdominal pain, biliary dilatation, enterocolitis, malignant gastrointestinal obstruction, neurotoxicity, decreased platelet count, thrombocytopenia, upper gastrointestinal haemorrhage and decreased white blood cell count (one patient in each case); in some patients more than one TEAE contributed to discontinuation.

[f] Refers to an adjustment in the dose of any of the four treatments administered.

[g] TEAEs leading to death, considered unrelated to treatment: cohort B, upper gastrointestinal haemorrhage (n = 1); cohort C, subdural haematoma (n = 1), dose-expansion cohort, malignant gastrointestinal obstruction (n = 1, considered unrelated to treatment), disease progression (n = 1, considered unrelated to treatment); considered related to treatment: cohort D, colitis (n = 1).

Serious TEAEs were reported for 17 patients (Table 2, Table A5) and were considered treatment-related in 10 patients (Table A6). Three patients died from TEAEs considered unrelated to treatment (Table 2).

TEAEs led to discontinuation (of oxaliplatin alone or all four study treatments) in eight patients and dose adjustments of any study treatment in 26 (Table 2). Sixteen patients received G-CSF (Table A8).

Clinically significant laboratory test abnormalities were reported as TEAEs. Laboratory and other safety assessment results were in line with the expected safety profile of the study regimen.

3.2.4. Efficacy

The median PFS was 9.2 months (95% CI: 7.69–11.96; Fig. 2A) in patients receiving the recommended dose. Fifteen patients had censored data, of whom one was still receiving treatment. The median OS was 12.6 months (95% CI: 8.74–18.69; Fig. 2B), with 20 deaths reported. Best overall response, ORR, DCR_{16} and DoR are reported in Table 3.

3.2.5. Other end-points

Results of PK and exploratory analyses are reported in the Appendix.

4. Discussion

Improvements in survival rates remain elusive for patients with pancreatic cancer [6,19], underscoring the need for improved treatment options [1]. To date, only one phase III trial of targeted therapy added to chemotherapy has shown improvement in survival for patients newly diagnosed with mPDAC [1,11,20–22], highlighting the need for more durable combination chemotherapy regimens as the backbone for future first-line treatment. In this phase I/II study, patients with locally advanced or mPDAC received a new combination first line: liposomal irinotecan 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 every 2 weeks (NALIRIFOX).

The safety of NALIRIFOX cannot be reliably compared with that of established therapies without head-to-head studies. However, no unexpected safety outcomes were apparent based on the known safety profiles of the drugs. Of the key TEAEs, grade ≥3 neutropenia was the most common among patients receiving the recommended dose (31.3%), followed by any grade of thrombo-embolic events (15.6%), then any grade of febrile neutropenia and grade ≥3 diarrhoea (12.5% for each). In addition, grade ≥3 neutrophil count decreased was reported in 12.5% of patients. G-CSF was administered to 50% of patients, to manage neutropenia or as prophylaxis in those considered high risk. G-CSF is permitted at the investigator's discretion in the ongoing NAPOLI-3 phase III study of NALIRIFOX (ClinicalTrials.gov NCT04083235; EudraCT 2018-003585-14). In the final long-term analysis of the NAPOLI-1 study, the most common grade ≥3 TEAEs (using MedDRA v14.1) [23] in patients receiving liposomal irinotecan + 5-FU/LV were neutropenia (32%; comprising neutropenia, neutrophil count

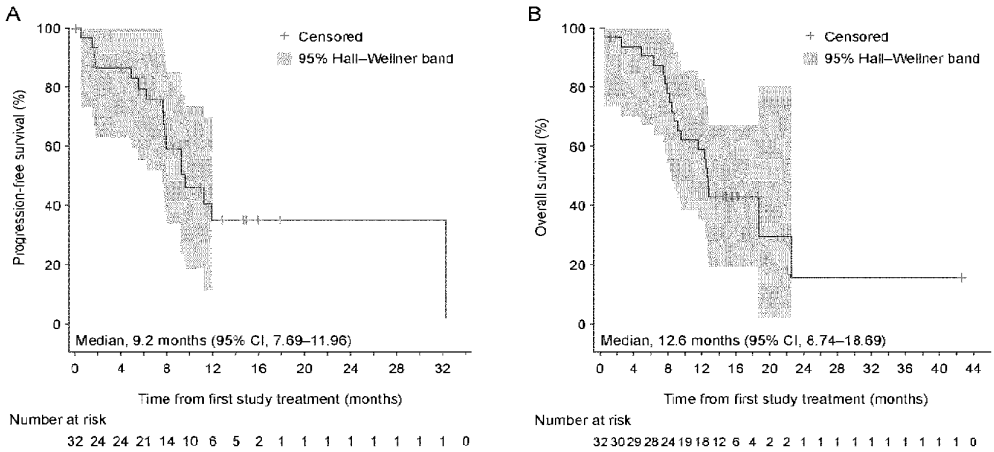

Fig. 2. (A) PFS and (B) OS in the pooled population of patients receiving the recommended dose (50/60[a]). Data are from the safety population (n = 32). Median PFS and OS were calculated using the Kaplan–Meier method, with 95% CIs calculated using Brookmeyer–Crowley methods. Confidence bands are 95% Hall–Wellner bands. One patient with minimal progressive disease per RECIST version 1.1 was approved for treatment continuation as the investigator believed there was a benefit from treatment. PFS for this patient ended at the date of minimal progressive disease. [a]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 (free-base equivalent) and oxaliplatin 60 mg/m^2, in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2, on days 1 and 15 of each 28-day cycle during either the dose-exploration or dose-expansion parts of the study. Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3
Clinical response.

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Best overall response[c], No. (%)						
CR	0	0	0	0	1 (4.0)	1 (3.1)[d]
PR	0	3 (42.9)	3 (30.0)	1 (14.3)	7 (28.0)	10 (31.3)
SD	2 (28.6)	3 (42.9)	1 (10.0)	3 (42.9)	12 (48.0)	15 (46.9)
PD	1 (14.3)	0	2 (20.0)	1 (14.3)	3 (12.0)	3 (9.4)
Non-PD/non-CR[e]	1 (14.3)	0	0	0	0	0
Not evaluable	3 (42.9)	1 (14.3)	4 (40.0)	2 (28.6)	2 (8.0)	3 (9.4)
Overall response (CR + PR), rate [95% CI][f]	0 [0, 41.0]	42.9 [9.9, 81.6]	30.0 [6.7, 65.2]	14.3 [0.4, 57.9]	32.0 [14.9, 53.5]	34.4 [18.6, 53.2]
DCR at 16 weeks (CR + PR + SD), rate [95% CI][g]	42.9 [9.9, 81.6]	71.4 [29.0, 96.3]	40.0 [12.2, 73.8]	28.6 [3.7, 71.0]	72.0 [50.6, 87.9]	71.9 [53.3, 86.3]
Duration of response[h]	(n = 0)	(n = 3)	(n = 3)	(n = 1)	(n = 8)	(n = 11)
Median, months [95% CI]	NE [NE, NE]	28.4 [3.52, NE]	NE [NE, 16.39]	NE [NE, NE]	9.4 [2.20, NE]	9.4 [3.52, NE]

Data are from the safety population and responses were determined using RECIST version 1.1.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 every on days 1 and 15 of each 28-day cycle.
[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.
[c] Best response recorded from the start of study treatment until disease progression or the start of new anti-cancer therapy.
[d] Patient received a diagnosis of locally advanced stage III disease.
[e] As per the protocol (version 1.0) at the time of their screening, one patient had a measurable lesion in a lymph node at screening that was too small to be considered a target lesion in accordance with RECIST version 1.1. Consequently, this patient was followed only for non-target lesions (included in the table above as 'non-PD/non-CR') but was included in the summary of overall response. The protocol was later amended to require the presence of target lesion(s).
[f] Proportion of patients with a CR or PR as the best overall response; 95% CIs were calculated using the Clopper–Pearson method.
[g] Proportion of patients with CR, PR or SD at the week-16 assessment; patients who died, whose tumours were no longer assessed, or who started new anti-cancer treatment before the week-16 assessment were not considered to have achieved disease control at week 16.
[h] Time from the first date of response (CR or PR) to the date of the first documented radiologically determined PD; duration of response was not calculated for patients who started a new anti-cancer treatment before the first response.

decreased, neutropenic sepsis, febrile neutropenia and several other terms), fatigue (14%), diarrhoea (13%) and vomiting (12%) [24]. Similarly, in the PRODIGE 4 study, the most common grade 3–4 TEAEs (using CTCAE v3.0) in patients receiving FOLFIRINOX were neutropenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhoea (12.7%) [5].

Grade ≥3 sensory neuropathy is a particular concern with oxaliplatin-containing regimens [25]. For the recommended NALIRIFOX regimen, none was reported. By contrast, in PRODIGE 4, grade 3–4 sensory neuropathy was experienced by 9.0% of patients receiving FOLFIRINOX (for persistent grade 2 sensory neuropathy, an oxaliplatin dose reduction from 85 to 65 mg/m^2 was permitted) [5].

The efficacy of first-line NALIRIFOX warrants further investigation, given a median PFS of 9.2 months (95% CI: 7.69–11.96) and median OS of 12.6 months (8.74–18.69), although direct comparisons with other studies cannot be made. The outcomes of the PRODIGE 4 study are of interest, as these underpin the recommendations for the FOLFIRINOX regimen as first-line therapy in mPDAC [2,10,11,26]. FOLFIRINOX was associated with a median PFS of 6.4 months (95% CI: 5.5–7.2) and median OS of 11.1 months (9.0–13.1), using RECIST v1.0 [5]. However, important differences between the study populations include the proportions of patients with metastatic disease at study entry (recommended NALIRIFOX regimen: 90.6%; FOLFIRINOX in PRODIGE 4: 100%), the proportions with liver metastases (43.8% and 87.6%, respectively) and the median ages (58 and 61 years, respectively) [5].

Limitations inherent in the present study design include the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomised design; and the absence of a control group. Although only patients with adequate performance status were included, similar restrictions were used in PRODIGE 4 [5].

5. Conclusions

The present phase I/II study demonstrated that first-line NALIRIFOX had tolerability that was generally manageable for patients with locally advanced or

mPDAC, with no unexpected safety outcomes. Ultimately, an important, as-yet-unanswered question is the preferred treatment for patients newly diagnosed with mPDAC. NAPOLI-3, an ongoing, large randomised, controlled, phase III study, will compare the efficacy (primary endpoint, OS) and safety of first-line NALIRIFOX with gemcitabine/nab-paclitaxel in this population, using the doses established here.

Clinical trial information

ClinicalTrials.gov number, NCT02551991 (https://www.clinicaltrials.gov/); EudraCT 2015-003086-28 (https://www.clinicaltrialsregister.eu/).

Data sharing statement

If patient data can be anonymised, Ipsen will share all individual patient data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months, and ending 5 years, after publication; after this time, only raw data may be available.

Funding

This study was sponsored by Ipsen. The sponsor was involved in the design of the study, analysis and interpretation as well as review of the manuscript.

Author contributions

Conception and design: A. Wainberg, Bruce Belanger, Fiona Maxwell, Tiffany Wang, Bin Zhang and Andrew Dean.

All authors: acquisition, analysis or interpretation of data for the work.

All authors: drafting the work or revising it critically for important intellectual content.

All authors: final approval of the manuscript.

All authors are accountable for all aspects of the work.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Note**: relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution.

Zev A. Waiuberg: Consulting or Advisory Role: AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Ipsen, Merck, QED Therapeutics, **Research Funding:** Five Prime Therapeutics (Inst), Ipsen (Inst), Novartis (Inst), Plexxikon (Inst).

Tanios Bekaii-Saab: 1Globe Health Institute, AbGenomics, Amgen, Array BioPharma, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Biomedical, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Exelixis, Genentech, Immuneering, Imugene, Incyte, Ipsen, Merck, Pancreatic Cancer Action Network (PanCAN), Seattle Genetics, Sobi, Sun BioPharma, Treos Bio.

Patrick M. Boland: Consulting or Advisory Role: Bayer, Merrimack Pharmaceuticals; honoraria: Sirtex Medical, **Research Funding:** Advaxis, Bayer, Boehringer Ingelheim, Boston Biomedical, Cascadian Therapeutics, Genentech, Merck

Farshid Dayyani: Research Funding: Amgen (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Exelixis (Inst), Ipsen (Inst), Taiho Pharmaceutical (Inst), **Consulting or Advisory Role:** Eisai, Exelixis, Foundation Medicine, Genentech, Ipsen, Natera (Signatera), QED Therapeutics, **Speakers' Bureau:** Amgen, Deciphera Pharmaceuticals, Eisai, Exelixis, Ipsen, Natera (Signatera), Sirtex Medical, **Employment:** Roche Diagnostics (I).

Teresa Macarulla: Honoraria: Eli Lilly, Ipsen, Roche, Sanofi, Sanofi Genzyme, Shire, Tesaro, **Research Funding:** AstraZeneca, Agios, Aslan Pharmaceuticals, Bayer, Biogen, Celgene, Eli Lilly, Genentech, Halozyme Therapeutics, Immonomedics, Merrimack Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Novocure, OncoMed Pharmaceuticals, Pfizer, Pharmacyclics, Roche, **Consulting or Advisory Role:** Baxalta, Celgene, H3 Biomedicine, Incyte, QED Therapeutics, Sanofi Genzyme, Shire, Servier, **Speakers' Bureau:** Celgene, Sanofi, Shire, **Travel, Accommodation, Expenses**: Bayer, H3 Biomedicine, Merck, Sanofi.

Kabir Mody: Research Funding: Agios, ArQule, AstraZeneca, Genentech, Incyte, Puma Biotechnology, Senwa Biosciences, Taiho Pharmaceutical, NCI of the NIH award # NCI/NIH P50 CA210964, **Consulting or Advisory Role:** AstraZeneca, Bayer, Celgene, Eisai, Exelixis, Ipsen, Merrimack Pharmaceuticals, Vicus Therapeutics.

Bruce Belanger: Former employee: Ipsen.

Fiona Maxwell: Employment: Ipsen, **Stock and Other Ownership Interests:** Ipsen.

Yan Moore: Employment: Ipsen, **Stock and Other Ownership Interests:** Ipsen, **Leadership:** Ipsen.

Arunthathi Thiagalingam: Former employee: Ipsen, **Stock and Other Ownership Interests:** Ipsen.

Tiffany Wang: Employment: Ipsen, **Stock and Other Ownership Interests:** Ipsen.

Bin Zhang: Employment: Ipsen, **Stock and Other Ownership Interests:** Ipsen, **Patents, Royalties, Other Intellectual Property:** Ipsen.

Andrew Dean: Consulting or Advisory Role: Shire (not compensated), Specialised Therapeutics (not compensated), **Travel, Accommodation, Expenses**: Amgen.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.03.028.

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Opposition to EP 3 337 478 of Ipsen Biopharm Ltd.

Declaration of Dr. Bin Zhang

I, Bin Zhang, MD, MSc, do solemnly and sincerely declare as follows:

1. I am a Vice President and Global Asset Lead at Ipsen. I have been an employee of Ipsen since 2016 and am involved in developing new oncology medication from conception through pre-clinical trials to clinical trials, and in NDA submissions.
2. I earned a MD Medical degree at China Medical University, Shenyang, and have held various clinical research and development roles since then. A copy of my curriculum vitae is attached as Annex A.
3. I have been closely involved in the planning, development, and execution of studies supporting the Onivyde® preclinical and clinical development program. I am familiar with the subject matter described in the above identified European patent.
4. This declaration is provided to show a subset of the results from the publication: "First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study", Wainberg et al, European Journal of Cancer, 151 (2021) 14-24. I am one of the authors named on this publication. I directly contributed to the work underlying this paper through my role at Ipsen, and am familiar with the contents.
5. Wainberg et al provides efficacy results from the phase I/II study of "NALIRIFOX", with a median progression-free survival (PFS) value of 9.2 months (95% CI: 7.69-11.96) and a median overall survival (OS) value of 12.6 months (95% CI: 8.74-18.69) for the pooled population[1]. The pooled population of the Wainberg et al study included patients at tumor stages IIA, III and IV at diagnosis[2]. Stage IV disease is also known as metastatic disease. The subset data provided in Annex B is a subpopulation analysis of the data in Wainberg et al, which confirm that these efficacy results apply also to the pooled population from Table 1 of Wainberg et al, when limited to the 29 patients with metastatic (stage IV) disease status when entering the study.
6. The results in Table 1 of Annex B show that overall median PFS for this subpopulation was 9.2 months (95% CI: 7.69-11.96)[3], which is identical to the value reported for the entire population in

[1] Section 3.2.4 on page 20 of Wainberg et al.
[2] See footnote d of Table 1 on page 18 of Wainberg et al. One patient in the dose-expansion cohort received a diagnosis of stage IIA disease, but entered the study with stage IV disease. Therefore, there were 29 patients in Wainberg et al. with stage IV disease: the 28 patients with stage IV disease at diagnosis, and the one patient with stage IIA disease at diagnosis but stage IV disease when entering the study.
[3] See page 2 of Annex B, final row of the table ("Overall"), pooled cohort.

Wainberg et al. Table 2 shows that median OS for this subpopulation was 12.7 months (95% CI: 8.74-19.12)[4], which is in fact comparable to the value reported for the entire population in Wainberg et al. These data show that the values of PFS and OS are at least as good for the metastatic patient subgroup versus the full study population in Wainberg et al. The small reduction in cohort size for this subgroup has almost no impact on the values, nor the confidence intervals associated with these values.

I believe that the facts that I have stated in this declaration are correct. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Bin ZHANG

Bin Zhang

December 6, 2021

Date

Annexes A. Curriculum Vitae

B. Metastatic patient subgroup population results

[4] See page 3 of Annex B, final row of the table ("Median Kaplan-Meier Estimates"), pooled cohort.

ANNEX A

BIN ZHANG MBBS, MMED, MSC

PROFESSIONAL EXPERIENCE

Ipsen Bioscience *Boston, MA*

Vice President, Global Asset Lead, Oncology, October 2020 -
Vice President, Oncology Development, October 2018 – October 2020
Senior Director/Global Development Lead, Oncology, September 2016 – September 2018

- Full development lead and global asset lead for oncology and rare disease assets. Core responsibilities include:
  - Provide leadership for a global team across R&D and commercial organizations, including clinical research, clinical operation, biostatistics, regulatory affairs, medical affairs, drug safety, biomarker/translational research, marketing and sales, market access, project management, health economics and outcomes research (HEOR), pharmaceutical development, chemistry, manufacturing, and controls (CMC), etc.
  - Define global development and commercial strategies for both monotherapy and combination regimens in multiple types of cancer and rare diseases, including pancreatic cancer, lung cancer, breast cancer, colon rectal cancer, biliary track cancer, pediatric solid tumors, pituitary tumors, etc.
  - Manage resource and budget for an organization with more than 80 full time employees; achieve multiple program milestones ahead of schedule
  - Lead the team on interactions with regulatory agencies worldwide, including US FDA, EMA, and Japan PMDA, including both in-person meetings and written communications. Successfully obtained fast track designations for multiple indications from US FDA
  - Work closely with key opinion leaders and developed strong collaborations through clinical research, engagement with regulatory agencies, and publications
  - Sever as the Ipsen representative in the Jointed Development Committee with external development partners; reached critical alignment on clinical development and regulatory interaction strategies
  - Hire and supervise project teams, develop, mentor and retain direct and indirect reports, and foster collaborative culture within cross-functional teams
  - Participate business development activities, including engagement with leading scientists/clinical experts, due diligence assessment and negotiation process; with a focus on in-licensing assets

KBP Biosciences *Princeton, NJ*

Senior Vice President of Clinical Research and Operation, July 2015 – September 2016

- Oversee all aspects of KBP's clinical development and operations across multiple compounds in early development phase. Key responsibilities include:
  - Provided clinical leadership and develop development strategy for all KBP compounds in multiple therapeutic areas, including cardiovascular disease and infectious disease.
  - Designed clinical study protocol and led clinical development and operation team to conduct multiple First-in-Human and Phase 2 studies (completed 4 studies on time or ahead of schedule)
  - Served as medical monitor to implement safety strategy across studies, including regular safety review and timely response to safety issues
  - Analyzed and interpreted clinical trial results, develop clinical study report, and develop publications

- Developed clinical sections of key regulatory documents, including IND applications, investigator brochures, DSUR, FDA annual report, etc. Successfully obtained qualified infectious disease product (QIDP) designation from US FDA
- Represented the company at external meetings with academic thought leaders, study investigators, investors, and regulatory agencies.
- Ensured effective communication with internal colleagues from different functional teams (e.g., discovery/translational medicine, regulatory and medical affairs, biostatistics, pharmacosurveillance, compliance and quality assurance, and CMC)
- Managed external collaboration with contract research organizations (CROs), thought leaders, and academic institutions
- Provided day-to-day management of clinical development and operation team, developed and mentored staff (both performance evaluation and career development)
- Served as a member of the corporate executive team and participate in key business decision, strategic planning, and evaluation of potential business development opportunities

Bristol-Myers Squibb *Princeton, NJ*

Director, Global Clinical Research, 2012 - 2015

- Full development role as global indication lead for immuno-oncology and diabetes compounds. Core responsibilities include:
  - Designed and implemented clinical development plans for multiple indications, including melanoma, prostate cancer, multiple myeloma, etc.
  - Served as the development lead for YERVOY® (ipilimumab) prostate cancer indication
  - Designed phase 1 to phase 3 clinical studies, developed study protocols and data monitoring committee (DMC) charter, and successfully gained approval from regulatory agencies
  - Served as study director and medical monitor for multiple global clinical studies
  - Analyzed data, developed clinical study report, and prepared publications
  - Regulatory interactions with US FDA, EMEA, PMDA (Japan), and CFDA (China)
  - Developed regulatory documents for NDA and BLA submissions and successfully gained US FDA approvals
  - Developed investigator brochure, risk management plans, and DSUR, primarily focusing on clinical efficacy and safety
  - Managed cross-function study teams, including members from clinical operation (both internal operation and external CRO), statistics, data management, drug supply, and medical publication
  - Engaged key opinion leaders (KOLs) and organized advisory board meetings

Director, Global Health Economics and Outcomes Research (HEOR) Oncology, 2011 - 2012

- Global HEOR lead and co-chair of market access team for elotuzumab (a humanized monoclonal antibody approved by FDA for the treatment of multiple myeloma)
  - Led a global, prospective, observational study (PREAMBLE). Major activities included designing study protocol and CRF and obtaining regulatory agency's approval, developing data analysis plan, interacting with thought leaders/investigators, establishing an external scientific advisor council including 10 global leading thought leaders, and overseeing operational activities, etc.
  - Generated evidence that demonstrates the association between treatment effects of progression free survival and overall survival among patients with multiple myeloma
  - Conducted early cost effectiveness assessment to support pivotal trial planning

Associate Director, US Medical, 2010 - 2011

- US HEOR lead for Onglyza®, Kombiglyze XR®, and Forxiga
  - Designed and conducted comparative effectiveness research of saxagliptin plus metformin vs. sulfonylurea (SU) plus metformin
  - Developed and ensured timely delivery of the AMCP dossier for Kombiglyze XR, one of the key deliverables for Kombiglyze XR launch in the US
  - Developed and executed the hypoglycemia communication strategy that demonstrates humanistic and economic burden of hypoglycemia through multiple publications

Abt Bio-Pharma Solutions, Inc. (Subsidiary of Abt Associates, Inc.) *Lexington, MA*
Associate Director, 2009 - 2010

- Conceptualized, designed, and implemented clinical and health outcomes research, including patient reported outcome research in clinical trials, cost effectiveness studies, systemic literature review, etc.
- Advised leading pharmaceutical, biotech, and medical device companies on product development and reimbursement strategies
- Served as the primary liaison with both US and international sponsors and effectively managed client interactions and ensured client satisfaction
- Supervised project teams, mentored junior staff, and implemented the strategy with teams
- Developed publication strategies and led manuscript/abstract development

Boston Health Economics, Inc. (BHE) *Waltham, MA*
Project Lead, 2006-2009

- Led research teams to conduct clinical and health economic research in various disease areas including cancer, cardiovascular disease, diabetes, infectious diseases, musculoskeletal diseases, bleeding disorders, etc.
- Designed and conducted prospective and retrospective economic evaluations of clinical trials
- Developed health economic models, including decision tree, Markov, and discrete event models and conducted multivariate probabilistic sensitivity analyses
- Designed and performed large-scale database analyses (e.g., National Health and Nutrition Examination Survey [NHANES], Premier Perspective database, and health insurance claims databases)
- Authored and co-authored multiple publications in the medical literature

New England Healthcare Institute (NEHI) *Cambridge, MA*
Research Associate, 2004-2006

- Performed health technology assessment and policy research
- Published two technology assessment reports on diabetes care
- Conducted research interviews with healthcare experts at academic institutes, biopharma and medical device companies, insurance companies, and government agencies

EDUCATION AND MEDICAL TRAINING

Harvard University, School of Public Health (HSPH) *Boston, MA*
Master of Science in Health Policy and Management, 2003- 2005 (GPA: 3.84/4.0)

- Received full scholarship
- Conducted medical decision science research at Harvard Center for Risk Analysis

Peking Union Medical College Hospital (PUMCH) *Beijing, China*
The most prestigious hospital in China, founded by the Rockefeller Foundation in 1921

Chief Resident in endocrinology, 2002-2003
Master of Medicine, 2002
Fellowship in endocrinology, 1999-2002
Resident in internal medicine, 1997-1999
Medical Internship, 1996-1997

- Received 7 years of extensive medical training in a leading academic medical center in China
- Obtained Master of Medicine (MMed), Internal Medicine, from Peking Union Medical College (PUMC) - a postgraduate academic degree awarded by medical schools to physicians following 2 years of instruction, examination, and complementing an existing fellowship in internal medicine.
- Took the leadership role of Chief Resident by managing all admissions and consults to the endocrinology department, supervising junior residents and interns, and organizing educational conferences
- Participated in designing and overseeing national epidemiologic studies and multi-center clinical trials
- Published four articles in peer-reviewed journals

China Medical University (CMU) *Shenyang, China*
Top 10 medical schools in China
MBBS (equivalent to MD in US), 1992-1997

- Graduated with high honor; in top 2 percent of a class of 400 students

PUBLICATIONS IN PEER-REVIEWED JOURNALS

1. Paz-Ares LG, Spigel DR, Chen Y, Jove M, Juan O, Rich P, Hayes T, Gutiérrez Calderón V, Bernabe R, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang T, Nazarenko N, Ponce S, Bunn P, RESILIENT Part 1: A Phase II Dose-Exploration and Dose-Expansion Study of Second-line Liposomal Irinotecan Monotherapy in Adults with Small Cell Lung Cancer. *Currently under peer reviewed by Cancer*
2. Karl Brendel K, Bekaii-Saab T, Boland PM, Dayyani F, Dean A, Macarulla T, Maxwell F, Mody K, Pedret-Dunn A, Wainberg ZA, **Zhang B**. Population Pharmacokinetics of Liposomal Irinotecan in Patients With Cancer and Exposure–Safety Analyses in Patients With Metastatic Pancreatic Cancer. *Accpeted by Pharmacometrics & Systems Pharmacology,* 2021 Nov 8. doi: 10.1002/psp4.12725.
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10. **Zhang B**, Donga PZ, Corral M, Sasane M, Miller JD, and Pashos CL. Pharmacoeconomic Considerations in Treating Iron Overload in Patients with β-thalassemia, Sickle Cell Disease, and Myelodysplastic Syndromes in the United States: A Literature Review. *PharmacoEconomics.* 2011, 29(6): 461-474.
11. Curkendall SM, **Zhang B**, Oh KS, Williams SA, Pollack MF, and Graham JP. Incidence and Cost of Hypoglycemia among Patients with Type 2 Diabetes. *Journal of Clinical Outcome Management.* 2011; 18(10): 455-462
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17. **Zhang B**, Xia WB, Xiang HD, Ming L, Yang AM, Zhang TP, and Yang T. Insulinoma manifested by hyperproinsulinemia: one case report. *Chinese Journal of Endocrinology and Metabolism*. 2003; 19 (6): 499-500.
18. **Zhang B** and Xiang HD. The Retrospective Analysis of Chronic Diabetic Complication in Type 2 Diabetes In-patients of PUMCH, *Beijing Medical Journal*, 2003; 25(2):9-14.
19. **Zhang B**, Xiang HD, Mao W, Guo XH, Wang JC, Jia WP, Yu M, Li QF, Fu ZY, Cao WH, and Qian RL. Epidemiological Survey of Chronic Vascular Complications of Type 2 Diabetic In-patients in Four Municipalities. *Acta Academiae Medicinae Sinicae*. 2002; 24 (5): 452-456.
20. **Zhang B**, Xu KF, and Lin YG. Allergic Bronchopulmonary Aspergilosis. *Chinese Journal of Tuberculosis and Respiratory*. 1999; 22(6): 377-378.

ANNEX A

SELECTED PRESENATIONS AT SCIENTIFIC CONFERENCES

1. Kokhreidze J, Harrow B, Ivanescu C, Whitsett J, Yao V, **Zhang B**. Psychometric properties of patient reported outcome (PRO) instruments in patients with small cell lung cancer (SCLC) in RESILIENT Part 1. Presented at the 57th American Society of Clinical Oncology (ASCO) Annual Meeting, 2021
2. Paz-Ares LG, Spigel DR, Chen Y, Jove M, Juan O, Rich P, Hayes T, Gutiérrez Calderón V, Bernabe R, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang T, Nazarenko N, Ponce S, Bunn P, RESILIENT part 1: a phase II dose-exploration and dose-expansion study of second-line liposomal irinotecan monotherapy in adults with small cell lung cancer. Presented as postal presentation at the International Association for the Study of Lung Cancer (IASLC), World Conference on Lung Cancer (WCLC) 2020.
3. Paz-Ares LG, Spigel DR, Chen Y, Jove M, Juan O, Rich P, Hayes T, Gutiérrez Calderón V, Bernabe R, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang T, Nazarenko N, Ponce S, Bunn P, RESILIENT part 2: a phase 3 study of liposomal irinotecan in patients with small cell lung cancer in the second-line setting. Presented as postal presentation at IASLC WCLC 2020
4. Wainberg Z, Bekaii-Saab T, Boland PM, Dayyani F, Macarulla T, Mody K, Belanger B, Maxwell F, Moore Y, Thiagalingam A, Wang T, **Zhang B**, Dean A, First-line liposomal irinotecan plus 5 fluorouracil/leucovorin plus oxaliplatin (NALIRIFOX) in adults with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC): a non-randomised, open-label, dose-exploration and dose-expansion phase 1/2 study. Presented as oral presentation at the 22nd European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, 2020.
5. Spigel DR, Paz-Ares LG, Chen YB, Jove M, Juan-Vidal O, Rich P, Hayes TM, Calderon MVG, Caro RB, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang HF, Kokhreidze J, Nazarenko N, Aix SP, Bunn P, RESILIENT part I, an open-label, safety run-in of liposomal irinotecan in adults with small cell lung cancer (SCLC) who have progressed with platinum-based first-line (1L) therapy: Subgroup analyses by platinum sensitivity. *Journal of Clinical Oncology, 38: 2020 (suppl; abstr 9069).* Presented at the 56th ASCO Annual Meeting, 2020
6. Waingberg Z, Bekaii-Saab T, Hubner R, Macarulla T, Paulson AS, Cutsem EV, Maxwell F, Moore Y, Wang HF, **Zhang B**, O'Reilly EM, NAPOLI-3: An open-label, randomized, phase III study of first-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma. *Journal of Clinical Oncology, 38: 2020 (suppl; abstr TPS4661).* Presented at the 56th ASCO Annual Meeting, 2020
7. Paz-Ares LG, Spigel DR, Chen YB, Jove M, Juan-Vidal O, Rich P, Hayes TM, Calderon MVG, Caro RB, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang HF, Kokhreidze J, Aix SP, Bunn P, RESILIENT part II: an open-label, randomized, phase III study of liposomal irinotecan injection in patients with small-cell lung cancer who have progressed with platinum-based first-line therapy. *Journal of Clinical Oncology, 38: 2020 (suppl; abstr TPS9081).* Presented at the 56th ASCO Annual Meeting, 2020

8. Paz-Ares LG, Spigel DR, Chen Y, Jove M, Juan O, Rich P, Hayes T, Gutiérrez Calderón V, Bernabe R, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang T, Nazarenko N, Ponce S, Bunn P, Initial Efficacy and Safety Results of Irinotecan Liposome Injection (nal-IRI) in Patients with Small Cell Lung Cancer. Presented as oral presentation at the 20th WCLC of IASLC, 2019
9. Anders C, Sachdev JC, Munster P, Northfelt D, Han HS, Ma C, Maxwell F, Wang T, Belanger B, **Zhang B**, Moore Y. Phase 1 Expansion Study of Irinotecan Liposome Injection (nal-IRI) in Patients with Metastatic Breast Cancer (mBC): Findings from The Cohort with Active Brain Metastasis (BM). *Neuro-Oncology Advances, 2019 1 (Supplement_1: i9).* Presented as oral presentation at Society for Neuro-Oncology's Inaugural Conference on Brain Metastases, 2019
10. Weinberg Z, Boland P, Lieu C,3 Dayyani F, Macarulla T, **Zhang B**, Belanger B, Moore Y, Wang T, Maxwell F, Dean A. A Phase 1/2, Open-label, Dose-expansion Study of Liposomal Irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) and Oxaliplatin (OX) in Patients with Previously Untreated Metastatic Pancreatic Cancer (mPAC). Presented as oral presentation at the 21st ESMO World Congress on Gastrointestinal Cancer, 2019
11. Farshid Dayyani F, Boland P, Dean A, Lieu CH, Macarulla T, **Zhang B**, Belanger B, Moore Y, Wang T, Maxwell F, Weinberg T. CA 19-9 levels in patients with metastatic pancreatic adenocarcinoma receiving first-line therapy with liposomal irinotecan plus 5-fluorouracil/leucovorin and oxaliplatin (NAPOX). Presented at American Association Cancer Research (AACR) Pancreatic Cancer Meeting, 2019
12. Paz-Ares LG, Spigel DR, Zielinski C, Chen Y, Jove M, Juan-Vidal O, Chu D, Rich P, Hayes T, Calderón MVG, Caro RB, Navarro A, Dowlati A, **Zhang B**, Moore Y, Wang T, Nazarenko N, Ponce S, Bunn P. RESILIENT: Study of Irinotecan Liposome Injection (nal-IRI) in Patients with Small Cell Lung Cancer: Preliminary Findings from Part 1 Dose-defining Phase. *Journal of Clinical Oncology 2019 37:15(suppl, 8562-8562).* Presented at the 55th ASCO Annual Meeting, 2019
13. Sachdev JC, Munster P, Northfelt D, Han HS, Ma C, Maxwell F, Wang T, Belanger B, **Zhang B**, Moore Y, Anders C. Phase 1 Expansion study of Irinotecan Liposome Injection (nal-IRI) in Patients with Metastatic Breast Cancer. Presented at the 110th AACR Annual Meeting, 2019
14. Paz-Ares LG, Yang CH, Zielinski C, Novello S, Schwartsmann G, Spigel D, Griesinger F, Dowlati A, Small S, de Jong FA, **Zhang B**, Nazarenko N, Bunn P. Liposomal Irinotecan vs Topotecan in Patients with Small Cell Lung Cancer Who Have Progressed On/After Platinum-Based Therapy. Presented at the 19th IASLC WCLC Meeting, 2018
15. Dean A, Wainberg ZA, Ramanathan R, Boland P, Mody K, **Zhang B**, Belanger B, Jong F, Braun S. A phase 1/2, open-label dose-escalation study of liposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) in patients with previously untreated metastatic pancreatic cancer. *Journal of Clinical Oncology, 2018;36(15): 4111.* Presented at the 54th ASCO Annual Meeting, 2018
16. **Zhang B**, Tan XJ, and Wang YL. Pharmacological profile of KBP-5074, a novel non-steroidal, highly selective, mineralocorticoid receptor antagonisit (MRA) for the treatemnt of cardiorenal diseases. *American Journal of Kidney Disease*, 2016; 67 (5): A118. Presented at the 2016 National Kidney Foundation (NKF) Spring Clinical Meeting, 2016
17. Wang YL, Liu QM, and **Zhang B**. Antibacterial activity of KBP-7072 against clinical isolates of drug-resistant bacteria. Presented by the 2016 American Society of Microbiology (ASM) Microbe Meeting, 2016
18. Liu QM, Wang YL, and **Zhang B**. Effect of KBP-7072 on bacterial activity and survival in a Klebseilla pneumoniae-induced murine pneumonia model. Presented by the 2016 American Society of Microbiology (ASM) Microbe Meeting, 2016

19. Liu QM, Wang YL, and **Zhang B**. Effect of KBP-7072 on bacterial activity and survival in a S. pneumoniae-induced murine pneumonia model, Presented by the 2016 American Society of Microbiology (ASM) Microbe Meeting, 2016
20. Amin A, Lawson DH, Salama AK, Koon HB, Guthrie T, Thomas SS, O'Day SJ, Shaheen MF, **Zhang B**, Francis S, Hodi FS, A single-arm, open-label, phase II study to evaluate the safety of vemurafenib (Vem) followed by ipilimumab (Ipi) in BRAF V600-mutated metastatic melanoma. *Journal of Clinical Oncology, 2015; 33 (15): 9032.* Presented at the 51st ASCO Annual Meeting, 2015
21. **Zhang B**, Cartier S, Rosen VM, April Teitelbaum A, Zhang Y, Bartlett B, Kroog G, Mukhopadhyay P, Wagner S. Investigation of the Relationship Between Treament Effects on Progression Free Survival and Overall Survival in Clinical Trials of Multiple Myeloma Based on Published Literature (updated analysis). *Haematologica,* 2013; 98 (s1): 100. Presented at the 18th Congress of European Hemotogloy Association, 2013
22. **Zhang B**, Cella D, Durie BG, Kuter D, Moreau P, Bartlett JB, Kroog GS, and Wagner S. Design and Rationale of the Multiple Myeloma PREAMBLE Study: A Prospective, Non-intervational, Multi-center Cohort Study. *Value In Health. 2012*; 15(4): A210. Presented at the 17th International Society for Pharmacoecnomics and Outcomes Research (ISPOR) Annual International Meeting, 2012.
23. **Zhang B**, Cartier S, Rosen VM, April Teitelbaum A, Zhang Y, Bartlett B, Kroog G, Mukhopadhyay P, Wagner S. Investigation of the Association Between Treatment Effects On Progression Free Survival and Overall Survival in Multiple Myeloma Using Data From Published Literature. *Blood,* 2012; 120 (21): 4241. Presented at the 54th American Society of Hemotology Annual Meeting, 2012
24. Curkendall SM, **Zhang B**, Lenhart G, Thomson E, Bell K, Graham JP. Frequency of Hypoglycemia: Patients Receiving Saxagliptin plus Metformin vs. Sulfonylurea (SU) plus Metformin in Real-World Clinical Practice. Presented at the 94th Endocrine Society Annual Meeting, 2012.
25. Becker DL, Thayer SW, **Zhang B**, Skornicki M, Graham JP, Bell KF. Reduced Rates of Hypoglycemia lead to Cost Savings fro Type 2 Diabetic Patients Treated with Saxagliptin versus Sulphpnlyurea in Actual Clinical Practice. *Value In Health. 2012*; 15(4): A177. Presented at the 17th ISPOR Annual International Meeting, 2012.
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27. Williams SA, Buysman E, Hulbert E, Bergeson JG, and **Zhang B**, "Hemoglobin A1C Outcomes in Type 2 Diabetes Mellitus patients (T2DM) on Combination Oral Antidiabetic Drugs (OADs): Step-therapy, Loose-Dose and Fixed-Dose Combinations. *Diabetes Care*, 2011; 60(S1): A630. Presented at the 71st ADA Annual Meeting, 2011.
28. Curkendall SM, **Zhang B**, Oh KS, William SA, Pollack MF, and Graham JP. Direct Medical Cost of Hypoglycemia among Patients with Type 2 Diabetes in the United States. *Value In Health. 2011*; 14(3): A96. Presented at the 16th ISPOR Annual International Meeting, 2011.
29. William SA, Buysman E, Bergeson JG, and **Zhang B**. Healthcare Resource Utilization and Costs among Type 2 Diabetes Mellitus (T2DM) patients on Different Oral Antidiabetic Drugs (OAD) Combination Therapies. *Journal of Managed Care Pharmacy*, 2011; 17(3): 263. Presented at the 23rd Academy of Managed Care Pharmacy (AMCP) Annual Meeting, 2011.
30. **Zhang B**, Donga P, Corral M, Miller JD, and Pashos CL. Literature Review of the Economic Burden of Iron Overload Associated with β-thalassemia, Sickle Cell Disease, and Myelodysplastic Syndromes in the United States (US). *Value In Health. 2010*; 13(3): A208. Presented at the 15th ISPOR Annual International Meeting, 2010.

31. **Zhang B**, Menzin J, Friedman M, Defriesse R, Duczakowski C, and Grave R. Treatment Patterns and Costs of Lumbar Spine Surgeries in a US Hospital Setting. *The Spine Journal*, 2009; 9(10): S169-S170. Presented at the North American Spine Society (NASS) 24th Annual Meeting, 2009.
32. **Zhang B**, Menzin J, Lee DW, Friedman M, Korn JR, Kurhanewicz J, and Dan R. Potentially Avoided Surgeries in Men with Localized, Low-Risk Prostate Cancer Undergoing Active Surveillance: A Model-Based Analysis. *The Journal of Urology*, 2009; 181(4): S193. Presented at the American Urological Association (AUA) 2009 Annual Meeting, 2009.
33. Menzin J, **Zhang B**, Lee DW, Friedman M, Korn JR, Kurhanewicz J, and Dan R. Life Expectancy for Clinically Localized, Low-Risk Prostate Cancer Patients Undergoing Active Surveillance vs. Immediate Surgery: A Model-Based Analysis. *The Journal of Urology*, 2009; 181(4): S163. Presented at the AUA 2009 Annual Meeting, 2009.
34. Menzin J, Lang K, **Zhang B**, Korn JR, Simko RJ, Zachry WM, and Patel NV. Development of an Interactive Model to Evaluate the Economic Impact of CHD Events among Adults with Dyslipidemia from an Employer Perspective. *Value In Health. 2009*; 12(3): A27. Presented at the 14th ISPOR Annual International Meeting, 2009.
35. Menzin J, **Zhang B**, Cohen J, Lobo FS, Korn JR, Friedman M, and Neumann PJ. The Relationship Between Glycemic Control and Healthcare Resource Utilization Among Patients with Type 2 Diabetes Mellitus: An Analysis of Managed Care Data. *Journal of Managed Care Pharmacy*, 2008; 14(7): 692-693. Presented at the 2008 AMCP Educational Conference, 2008.
36. Menzin J, **Zhang B**, Neumann PJ, Lines LM, Polly DW, Barnett-Myers S, Fontes R, and Traynelis VC. The Economic Impact of the Prestige Cervical Disc System: Results from a Randomized Clinical Trial. *Journal of Neurosurgery*, 2008; 108(4): A864. Presented at the 6th American Association of Neurological Surgeons Annual Meeting, 2008. Reported by WashingtonPost.com, Forbes.com, USAToday.com, AOL.com, etc. and cited by U.S. Department of Health and Human Services.
37. Menzin J, **Zhang B**, Friedman M, Charland SL, and Burge RT. Effects of intensifying lipid-altering therapy on CHD patients in a secondary prevention population with high non-HDL cholesterol. *Value in Health*, 2008; 11(3): A244. Presented at the 13th ISPOR Research Annual International Meeting, 2008.
38. **Zhang B**, Menzin J, Tran MH, Neumann PJ, and Friedman M. The potential savings in operating room time associated with the use of sugammadex to reverse selected neuromuscular blocking agents: findings from a hospital efficiency model. *Value in Health,* 2008; 11(3): A187. Presented at the 13th ISPOR Annual International Meeting, 2008.
39. **Zhang B,** Hepner D, Tran MH, Friedman M, Korn JR, and Menzin J. Neuromuscular blockade, reversal agent use, and operating room time: an analysis of US hospital data. Presented at the 2008 American Society of Health-System Pharmacists (ASHP) Summer Meeting, 2008.
40. **Zhang B**, Friedman M, Charland SL, Burge RT, Simko RJ, and Menzin J. A Model-Based Analysis of the Effects of Intensifying Lipid-Altering Therapy on Direct Medical Costs of Coronary Heart Disease Events in a Secondary Prevention Population in the United States. *Value in Health*, 2007; 10(6): A411. Presented at the 10th ISPOR Annual European Congress, 2007.
41. Lee DW, Dann RA, Lintner MJ, **Zhang B**, Friedman M, and Menzin J. International incidence of men with uncertain indication for radical prostatectomy: an evidence-based analysis. *Value in Health*, 2007; 10(6): A339-340. Presented at the 10th ISPOR Annual European Congress, 2007.
42. Neumann PJ, Cohen JT, **Zhang B**, and Fillit HM. Cost-Effectiveness of Screening for Cognitive Impairment in Older Populations: Implications for Alzheimer's Disease Care. *Value in Health*. 2007; 10(3): A88. Presented at the 12th ISPOR Annual International Congress, 2007.
43. **Zhang B** and Xiang HD. The Retrospective Investigation of Chronic Diabetic Complications of Type 2 Diabetes in In-patients in PUMCH. *Diabetes Research and Clinical Practices*. 2002; 56 (S1): S156. Presented at the 5th International Diabetes Federation (IDF) Western Pacific Region Congress, 2002.

44. **Zhang B** and Xiang HD. The Prevalence of Chronic Diabetic Complications and Correlative Diseases of In-patients with Type 2 Diabetes in Four Municipalities. *Diabetes Research and Clinical Practices*. 2002; 56 (S1): S109-110. Presented at the 5th IDF Western Pacific Region Congress, 2002.

SELECTED PUBLICATIONS AND REPORTS IN NON-PEER REVIEWED JOUNALS

1. **Zhang B,** Nocon R, and Everett W. Insulin Analogs: Innovation in the Biotechnology, *NEHI publication*, January 2006.
2. Spurgeon S, Nocon R, **Zhang B**, et al. Continuous Glucose Monitoring: Innovation in the Management of Diabetes, *NEHI publication*, March 2005.

PATENT

U.S. Patent 11071726, "Treating gastric cancer using combination therapies comprising liposomal irinotecan, oxaliplatin, 5-fluorouracil (and leucovorin)," July 27, 2021

OTHER SERVICES

1. Guest lecturer, Department of Public Health Sciences at Clemson University, 2014-2017
2. Invited panelist, Medical Technology Assessment Committee of The Second Westlake Forum on Healthy China 2020: Policy and Action, 2009
3. Researcher, the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry, 2009

HONORS & AWARDS

1. Lyman and Grew Memorial Scholarship, Harvard University, 2003-2005
2. Outstanding Graduate Award, CMU, 1997
3. Scholarships for Academic Excellence, CMU, 1992-1997

Annex B

Table 1

Summary of Progression-Free Survival for Patients with Metastatic Status
(Safety Population)

	Dose Exploration Cohort				Dose Expansion Cohort	50mg/60mg Pooled
	Cohort A N = 4	Cohort B N = 6	Cohort C N = 8	Cohort D N = 5	N = 23	N = 29
Patients with PFS events [1], n(%)	2 (50.0)	2 (33.3)	3 (37.5)	4 (80.0)	13 (56.5)	15 (51.7)
Disease Progression	2 (50.0)	1 (16.7)	2 (25.0)	2 (40.0)	12 (52.2)	13 (44.8)
Death	0	1 (16.7)	1 (12.5)	2 (40.0)	1 (4.3)	2 (6.9)
Censored Patients [2], n(%)	2 (50.0)	4 (66.7)	5 (62.5)	1 (20.0)	10 (43.5)	14 (48.3)
No Baseline Tumor Assessments	0	0	0	0	0	0
Progression documented after new anti-cancer therapy	0	2 (33.3)	0	0	0	2 (6.9)
Death documented after new anti-cancer therapy	2 (50.0)	2 (33.3)	3 (37.5)	1 (20.0)	4 (17.4)	6 (20.7)
Progression documented after 16 weeks of baseline or the last non-PD tumor assessment	0	0	0	0	0	0
Death documented after 16 weeks of baseline or the last non-PD tumor assessment	0	0	0	0	1 (4.3)	1 (3.4)
Treatment discontinuation for clinical deterioration without documented progression or death	0	0	0	0	0	0

PFS: Progression-free Survival; CI: Confidence Interval; NE: Not Evaluable; nal-IRI: liposomal irinotecan.
Dose level A: oxaliplatin 60 mg/m^2 + nal-IRI 70 mg/m^2; Dose level B: oxaliplatin 60 mg/m^2 + nal-IRI 50 mg/m^2;
Dose level C: oxaliplatin 85 mg/m^2 + nal-IRI 50 mg/m^2; Dose level D: oxaliplatin 70 mg/m^2 + nal-IRI 55 mg/m^2.
50mg/60mg pooled cohort includes patients from both cohort B and expansion cohort. The dose for patients from pooled cohort is dose level B (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2). Nal-IRI dose is calculated in free-base equivalent.
Note: PFS time will be determined as the time from the date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first, in months.
[1] Only includes progression events per SAP 'PFS censoring rules'.
[2] Only includes censored events per SAP 'PFS censoring rules'.
[3] Calculated using Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method.
[4] CIs are calculated using Clopper-Pearson method.

Table 1 (cont'd)

Summary of Progression-Free Survival for Patients with Metastatic Status
(Safety Population)

	Dose Exploration Cohort				Dose Expansion Cohort	50mg/60mg Pooled
	Cohort A N = 4	Cohort B N = 6	Cohort C N = 8	Cohort D N = 5	N = 23	N = 29
Treatment discontinuation for AEs or other reasons without documented progression or death	0	0	2 (25.0)	0	5 (21.7)	5 (17.2)
New anti-cancer therapy started prior to the treatment termination without documented progression	0	0	0	0	0	0
New surgical cancer therapy started prior to the treatment termination without documented progression	0	0	0	0	0	0
Patient on treatment at time of analysis	0	0	0	0	0	0
None of above Progression/Death/Treatment Termination/New Anticancer Therapy Started/Cancer-related Surgery	0	0	0	0	0	0
Median progression-free Survival (95% CI) [3]						
Overall	6.3 (2.96, NE)	32.3 (0.53, NE)	1.9 (0.46, NE)	3.8 (1.22, NE)	9.2 (7.59, 11.20)	9.2 (7.69, 11.96)

PFS: Progression-free Survival; CI: Confidence Interval; NE: Not Evaluable; nal-IRI: liposomal irinotecan.
Dose level A: oxaliplatin 60 mg/m^2 + nal-IRI 70 mg/m^2; Dose level B: oxaliplatin 60 mg/m^2 + nal-IRI 50 mg/m^2;
Dose level C: oxaliplatin 85 mg/m^2 + nal-IRI 50 mg/m^2; Dose level D: oxaliplatin 70 mg/m^2 + nal-IRI 55 mg/m^2.
50mg/60mg pooled cohort includes patients from both cohort B and expansion cohort. The dose for patients from pooled cohort is dose level B (oxaliplatin 60 mg/m^2 + nal-IRI 50 mg/m^2). Nal-IRI dose is calculated in free-base equivalent.
Note: PFS time will be determined as the time from the date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first, in months.
[1] Only includes progression events per SAP 'PFS censoring rules'.
[2] Only includes censored events per SAP 'PFS censoring rules'.
[3] Calculated using Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method.
[4] CIs are calculated using Clopper-Pearson method.

Annex B

Table 2

Summary of Overall Survival for Patients with Metastatic Status
(Safety Population)

	Dose Exploration Cohort				Dose Expansion Cohort	50mg/60mg Pooled
	Cohort A N = 4	Cohort B N = 6	Cohort C N = 8	Cohort D N = 5	N = 23	N = 29
Patients Who Died n(%)	4 (100)	6 (100)	6 (75.0)	5 (100)	17 (73.9)	23 (79.3)
Patients with censored endpoint n(%)	0	0	2 (25.0)	0	6 (26.1)	6 (20.7)
Median Kaplan-Meier Estimates (months) (95% CI) [1]	9.2 (3.98, 13.70)	12.2 (0.53, 22.54)	16.6 (0.69, 21.75)	5.8 (1.35, 14.65)	12.7 (8.18, 23.66)	12.7 (8.74, 19.12)

CI: Confidence Interval; NE: Not Evaluable; nal-IRI: liposomal irinotecan.
Dose level A: oxaliplatin 60 mg/m^2 + nal-IRI 70 mg/m^2; Dose level B: oxaliplatin 60 mg/m^2 + nal-IRI 50 mg/m^2;
Dose level C: oxaliplatin 85 mg/m^2 + nal-IRI 50 mg/m^2; Dose level D: oxaliplatin 70 mg/m^2 + nal-IRI 55 mg/m^2.
50mg/60mg pooled cohort includes patients from both cohort B and expansion cohort. The dose for patients from pooled cohort is dose level B (oxaliplatin 60 mg/m^2 + nal-IRI 50 mg/m^2). Nal-IRI dose is calculated in free-base equivalent.
Notes: Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date prior to database lock.
The last known alive date will be identified as the latest qualifying date from examination of the Overall Survival CRF form, laboratory sample dates, adverse event start and stop dates, concomitant medication start and stop dates as well as normal visit/follow-up dates. The censored Overall Survival time will be computed as (date last known to be alive - date of the first study treatment + 1).
[1] Calculated using Kaplan-Meier technique. CIs for median overall survival are derived based on Brookmeyer-Crowley method.
[2] CIs are calculated using Clopper-Pearson method.

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed*: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a *short* axis of $\geqslant$15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. *History of RECIST criteria*

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. *Why update RECIST?*

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ⩾15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. *Specifications by methods of measurements*

3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

4.3.1. *Evaluation of target lesions*

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

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters 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 at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist *is* able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

4.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. *Best overall response: all time points*

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/- non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[71]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 in phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

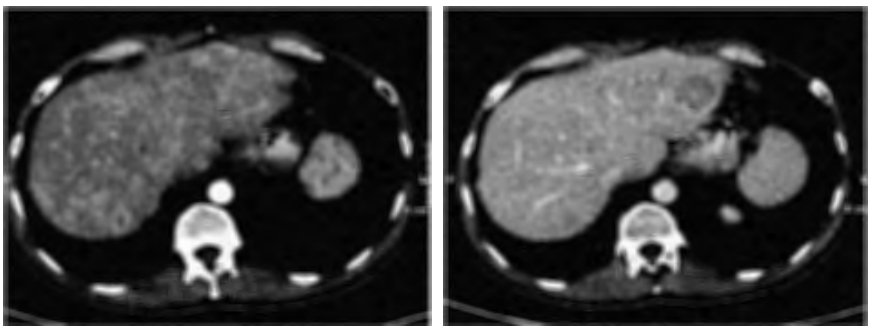

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

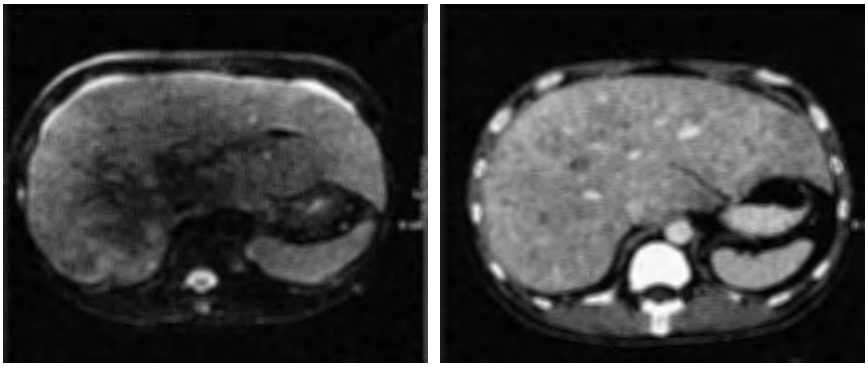

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials.*

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

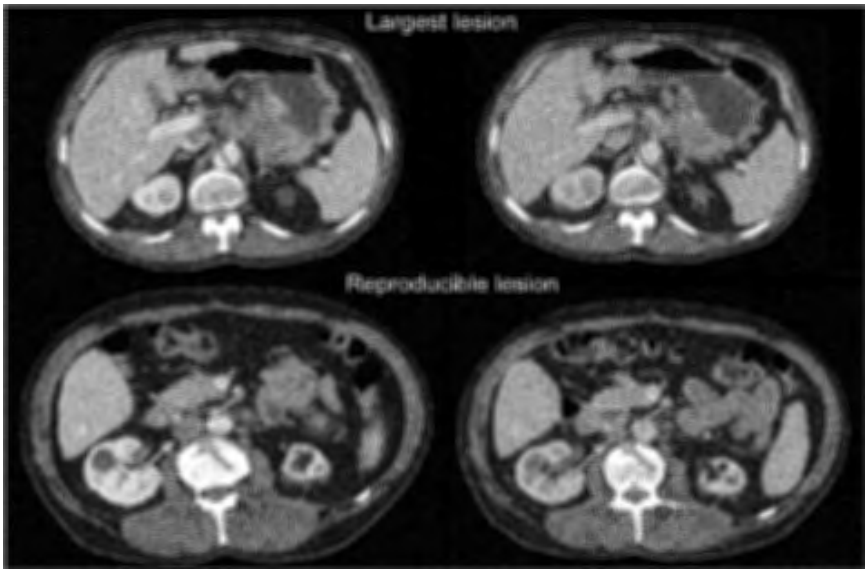

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

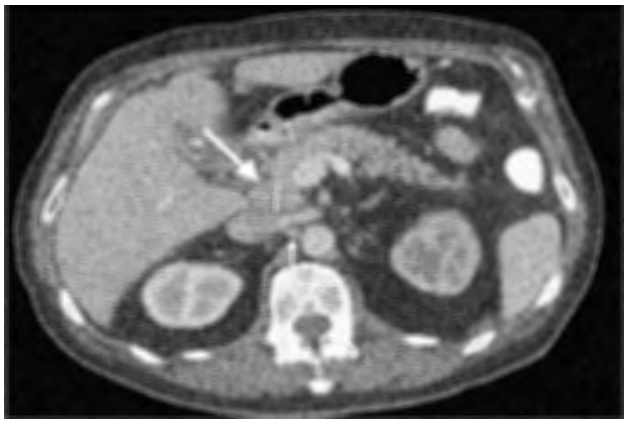

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

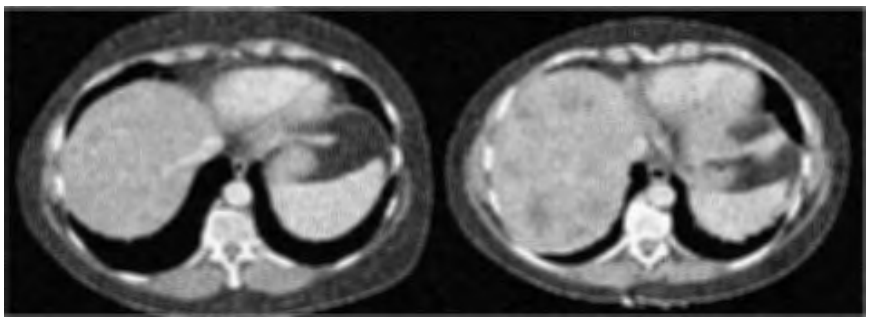

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

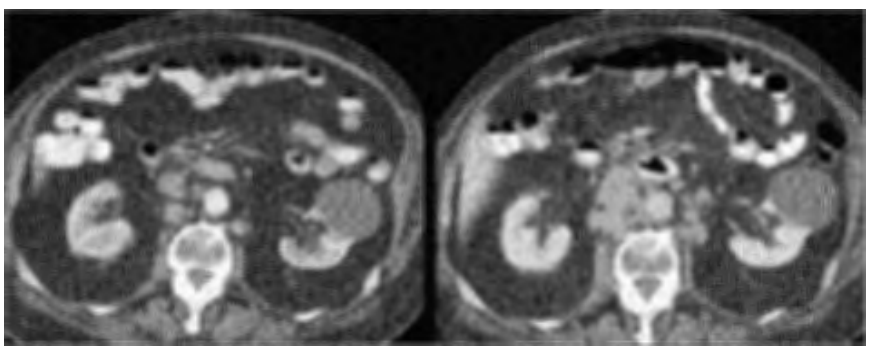

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(*continued on next page*)

Appendix III – *continued*

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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Original Article

Comparison of RECIST version 1.0 and 1.1 in assessment of tumor response by computed tomography in advanced gastric cancer

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Objective: Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0 (RECIST 1.0) was proposed as a new guideline for evaluating tumor response and has been widely accepted as a standardized measure. With a number of issues being raised on RECIST 1.0, however, a revised RECIST guideline version 1.1 (RECIST 1.1) was proposed by the RECIST Working Group in 2009. This study was conducted to compare CT tumor response based on RECIST 1.1 *vs.* RECIST 1.0 in patients with advanced gastric cancer (AGC).

Methods: We reviewed 61 AGC patients with measurable diseases by RECIST 1.0 who were enrolled in other clinical trials between 2008 and 2010. These patients were retrospectively re-analyzed to determine the concordance between the two response criteria using the κ statistic.

Results: The number and sum of tumor diameters of the target lesions by RECIST 1.1 were significantly lower than those by RECIST 1.0 ($P<0.0001$). However, there was excellent agreement in tumor response between RECIST 1.1 and RECIST 1.0 ($\kappa=0.844$). The overall response rates (ORRs) according to RECIST 1.0 and RECIST 1.1 were 32.7% (20/61) and 34.5% (20/58), respectively. One patient with partial response (PR) based on RECIST 1.0 was reclassified as stable disease (SD) by RECIST 1.1. Of two patients with SD by RECIST 1.0, one was downgraded to progressive disease and the other was upgraded to PR by RECIST 1.1.

Conclusions: RECIST 1.1 provided almost perfect agreement with RECIST 1.0 in the CT assessment of tumor response of AGC.

Keywords: Response Evaluation Criteria in Solid Tumors guideline version 1.0 (RECIST 1.0); Response Evaluation Criteria in Solid Tumors guideline version 1.1 (RECIST 1.1); gastric cancer; tumor response

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Introduction

Objective assessment of the change in tumor burden is a critical component in the evaluation of cancer therapeutics (1). The Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0 (RECIST 1.0) was proposed as a new guideline for evaluating tumor response. Key features of RECIST 1.0 include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10, a maximum of five per organ), and the use of uni-dimensional rather than bi-dimensional measures for evaluation of tumor burden (2). RECIST 1.0 has been widely accepted as a standardized measure of tumor response, particularly in oncologic clinical trials with objective response or time to progression as primary endpoints (3). However, a number of issues were

Table 1 Summary of major changes in RECIST 1.1 compared with RECIST 1.0

RECIST guideline	RECIST 1.1	RECIST 1.0
No. of target lesions	Up to 2 per organ, up to 5 in total	Up to 5 per organ, up to 10 in total
Assessment of LNs	Short-axis measurements should be used and recorded; ≥15 mm, target lesions; ≥10 mm but <15 mm, non-target lesions; <10 mm,non-pathological	No clear guideline provided
Clarification of disease progression	20% increase in the sum of target lesions and 5-mm absolute increase are required	20% increase in the sum of target lesions (no minimum absolute size increase) is required
FDG-PET scan	Included only in the detection of new lesions	Not included

RECIST 1.0, Response Evaluation Criteria in Solid Tumors guideline version 1.0; RECIST 1.1, Response Evaluation Criteria in Solid Tumors guideline version 1.1; LNs, lymph nodes; FDG, fluorodeoxyglucose; PET, positron emission tomography.

raised on RECIST 1.0, which included the total number of lesions to be assessed, the assessment of lymph nodes (LNs), and the utility of newer imaging technologies such as multi-detector computed tomography (MDCT) and positron emission tomography (PET) (4,5).

In 2009, a revised RECIST guideline version 1.1 (RECIST 1.1) was presented by the RECIST Working Group, based in part on investigations using a database consisting of more than 6,500 patients with about 18,000 target lesions (1,4,6,7). Major changes in RECIST 1.1 included LN measurement, the maximum number of target lesions, and the definition of disease progression (*Table 1*) (6-8).

The new criteria recommend measurement of LNs on their short axis and propose measurement rules for categorizing an LN that is at least 15 mm on its short axis to be considered a target lesion. An LN with at least 10 mm but less than 15 mm on its short axis, although it may be pathologic, is considered a non-target lesion. An LN with less than 10 mm on its short axis is regarded as normal. The maximum number of target lesions has been reduced from ten to five in total, and from five to two per organ. Disease progression has been clarified: an absolute increase of at least 5 mm as well as a 20% increase in sum is now required to be defined as progressive disease (PD).

RECIST 1.1 showed almost perfect agreement with REICST 1.0 in tumor response assessment of patients with non-small cell lung cancer (NSCLC) (9-11). However, it still remains to be revealed how RECIST 1.1 affects the selection and CT measurement of target lesions, assessment of tumor response, and time to progression in malignancies of other primary sites.

This study was conducted to compare the CT measurement and tumor response based on RECIST 1.1 *vs.* RECIST 1.0 in patients with advanced gastric cancer (AGC).

Patients and methods

Patients

This study was performed under an Institutional Review Board's waiver according to the Korean ethical guidelines for epidemiological research. We evaluated 61 AGC patients with at least one measurable disease by RECIST 1.0 who were enrolled in other clinical trials between 2008 and 2010 at Hallym University Sacred Heart Hospital, Anyang, Korea and Asan Medical Center, Seoul, Korea. The patient was eligible for this study if he or she met the following criteria: histologically confirmed adenocarcinoma or signet-ring cell carcinoma of the stomach, radiologically or histologically confirmed metastatic disease, having at least one measurable lesion by RECIST version 1.0, having no other cancers, no history of chemotherapy and/or radiotherapy, and tumor assessment by MDCT at baseline and post-chemotherapy. These patients had received the first-line chemotherapy with cisplatin plus capecitabine or oxaliplatin plus 5-FU/leucovorin.

CT tumor measurement

All CT scans were performed on a 64-MDCT scanner with a slice thickness of 5 mm, and the images were transferred to the Picture Archiving Communication System (PACS). The post-chemotherapy CT scans were performed every two cycles of cisplatin plus capecitabine and four cycles of oxaliplatin plus 5-FU/leucovorin.

The longest diameter of each target lesion was manually measured on an axial CT image using calipers as a measuring tool on PACS. The target lesion description and CT size measurement, the sum of the longest tumor diameters of target lesions for each imaging study, and

Characteristic	No. of patients	%
Median age, years [range]	58 [26-78]	
Gender		
Male	42	68.9
Female	19	31.1
Histology		
Well differentiation	5	8.2
Intermediated differentiation	17	27.9
Poorly differentiation	39	63.9
Measurable metastatic lesions		
Liver	8	13.1
Lung	2	3.2
Lymph node	51	83.6
Chemotherapy regimen		
Cisplatin plus capecitabine	21	34.4
Oxaliplatin plus 5-FU/leucovorin	40	65.6

tumor response for each patient were recorded by a board-certified abdomen radiologist using RECIST 1.0 and RECIST 1.1. Briefly, the target lesions recorded in the original measurements were reassessed if they met the criteria of RECIST 1.1: LNs less than 15 mm on the short axis were excluded from target lesions; when the number of target lesions exceeded the limits according to RECIST 1.1 (up to five in total and up to two per organ), smaller lesions were eliminated from target lesions; short-axis measurements were used for LNs instead of long-axis measurements.

The number of RECIST 1.0 and RECIST 1.1 target lesions and the sum of tumor diameters at baseline and first follow-up were each calculated and recorded. Tumor responses were assessed separately using RECIST 1.0 and RECIST 1.1, respectively.

Statistical analysis

A paired Student's *t*-test was used to assess the statistical significance of changes in the number of target lesions and the sum of lesion diameters at baseline between RECIST 1.0 and RECIST 1.1. A P value of less than 0.05 was considered statistically significant. Concordance between the tumor responses by RECIST 1.0 *vs.* RECIST 1.1 was assessed using the κ statistic. A kappa value of more than 0.75 was interpreted as showing excellent agreement.

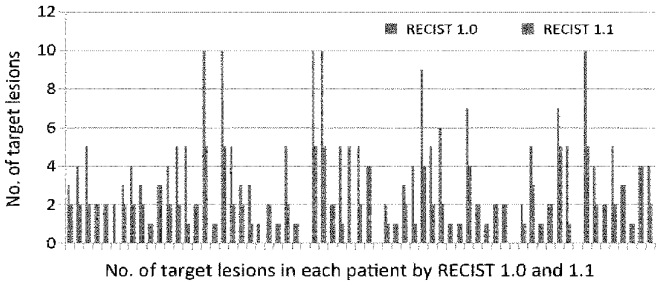

Figure 1 Number of target lesions according to Response Evaluation Criteria in Solid Tumors guideline version 1.0 (RECIST 1.0) *vs.* Response Evaluation Criteria in Solid Tumors guideline version 1.1 (RECIST 1.1). Number of target lesions by RECIST 1.1 was significantly lower than that by RECIST 1.0 (P<0.0001, paired Student's *t*-test).

Results

Patient characteristics

Patients' baseline characteristics are summarized in *Table 2*. The patients consisted of 42 male (68.9%) and 19 female patients with a median age of 58 years (range, 26-78 years). Thirty-nine patients (63.9%) had poorly differentiated adenocarcinoma, and five (8.2%) well differentiated adenocarcinoma. The most common metastatic site with measurable lesions was the LN (83.6%), followed by the liver (13.1%) and lung (3.2%). Forty patients (65.6%) received cisplatin plus capecitabine as a first-line chemotherapy, and the remaining 21 (34.4%) were treated with oxaliplatin plus 5-FU/leucovorin.

Number of target lesions and sum of tumor diameters

The number of target lesions on RECIST 1.1 was significantly lower than that on RECIST 1.0 (P<0.0001), with a decrease of target lesions in 38 patients (62.3%) (*Figure 1*). The median number of target lesions was 3 (range, 1-10) by RECIST 1.0 and 2 (range, 0-5) by RECIST 1.1, respectively. Three patients had no longer target lesion by RECIST 1.1 because their LN target lesions by RECIST 1.0 were excluded by the new LN size criteria of REICST 1.1 (at least 15 mm on its short axis). The numbers of target lesions decreased by RECIST 1.1 were one in eight patients, two in ten, three in nine, four in four, and five in seven, respectively.

The sum of diameters of the target lesions using

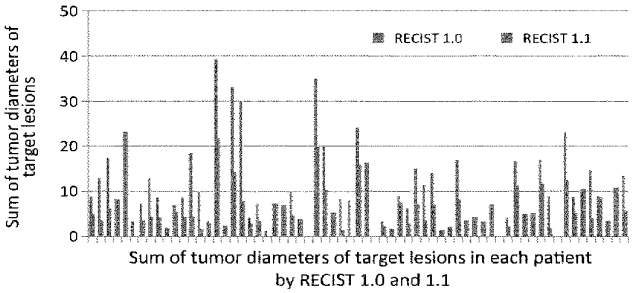

Figure 2 The sum of tumor diameters of target lesions according to Response Evaluation Criteria in Solid Tumors guideline version 1.0 (RECIST 1.0) *vs.* Response Evaluation Criteria in Solid Tumors guideline version 1.1 (RECIST 1.1). The sum of tumor diameters of target lesions by RECIST 1.1 was significantly lower than that by RECIST 1.0 (P<0.0001, paired Student's *t*-test).

RECIST 1.1 was also significantly lower than that using RECIST 1.0 (10.9±8.52 cm *vs.* 6.33±5.12 cm, P<0.0001) as a result of significant decreases in the target lesions (*Figure 2*).

Best tumor response

The comparison of tumor responses between RECIST 1.0 and RECIST 1.1 is shown in *Table 3*. There was an excellent agreement in the CT assessment of tumor response between RECIST 1.1 and RECIST 1.0, with a kappa value of 0.844. While tumor responses by RECIST 1.0 were 32.7% (20/61) of partial response (PR), 62.2% (38/61) of stable disease (SD), and 4.9% (3/61) of PD, respectively, and tumor responses by RECIST 1.1 were 34.5% (20/58) PR, 58.6% (34/58) SD, and 6.9% (4/58) PD. One patient with PR based on RECIST 1.0 was reclassified as SD by RECIST 1.1 because 4 LN target lesions with a short axis of less than 15 mm were excluded by RECIST 1.1. Of two patients with SD by RECIST 1.0, one was downgraded to PD and the other was upgraded to PR by the new criteria of up to two lesions per organ in RECIST 1.1.

Discussion

In this study, we compared CT tumor measurement and tumor response based on RECIST version 1.0 *vs.* 1.1 in patients with AGC who had received first-line chemotherapy with cisplatin plus capecitabine or oxaliplatin plus 5-FU/leucovorin. Our results showed that RECIST 1.1 significantly decreased the number of target lesions as well as the sum of tumor diameters of the target lesions in AGC

Best response by RECIST 1.0	Best response by RECIST 1.1			
	Progressive disease	Stable disease	Partial response	Non-evaluable
Progressive disease	3	0	0	0
Stable disease	1	33	1	3
Partial response	0	1	19	0
Non-evaluable	0	0	0	0

RECIST 1.0, Response Evaluation Criteria in Solid Tumors guideline version 1.0; RECIST 1.1, Response Evaluation Criteria in Solid Tumors guideline version 1.1.

patients at baseline of the first-line chemotherapy. However, the best tumor response assessment showed almost perfect agreement between two RECIST versions.

The decreases on the number of target lesions and the sum of tumor diameters of the target lesions were mainly resulted from the following two reasons. The first is a decrease in the number of LN target lesions due to the new size criteria of malignant LN by RECIST 1.1 (LNs only ≥15 mm in the short axis are considered measurable and assessable as target lesions). This new LN criteria of RECIST 1.1 affected 27 patients (44.3%) in our study. Of 61 patients who had at least one target lesion according to RECIST 1.0 at baseline of the first-line chemotherapy, interestingly, 3 (4.9%) had no longer target lesions by RECIST 1.1 with the new LN criteria. If a study using RECIST 1.1 had been planned, these patients would have been excluded from clinical trials. In another study of patients with AGC, Fuse *et al.* reported that the proportion of patients with target lesions was significantly decreased from 67% to 53% by the new LN criteria (12). These results indicate that RECIST 1.1 may alter the eligibility of patients for clinical trials in which overall response rate (ORR) is a primary end point. In this study, since patients had been enrolled in other clinical trials of which primary end point was overall responses, they all had at least one measurable disease at baseline according to the eligibility criteria by RECIST 1.0. Unlike in the study by Fuse *et al.*, therefore, we had no opportunity to compare the proportions of patients with at least one target lesion between RECIST 1.0 and 1.1 in all consecutive patients with AGC.

Another cause of the decrease in the number of target lesions and the sum of tumor diameters was the change in

the maximum number of target lesions per organ (from a maximum of ten to a maximum of five and from five per organ to two per organ). In this study, 8 patients had more than 3 target lesions in an organ according to RECIST 1.0. Using RECIST 1.1, however, the sum of diameters of target lesions by RECIST 1.0 was decreased in 35 patients (57.4%). This decrease in the sum of tumor diameters was mostly due to the decrease in the number of target lesions.

In this study with AGC patients who received the first-line chemotherapy with cisplatin plus capecitabine or oxaliplatin plus 5-FU/leucovorin, two RECIST versions showed almost perfect agreement in the evaluation of the best tumor response by CT (κ=0.844). The ORRs according to RECIST 1.0 and RECIST 1.1 were 32.7% (20/61) and 34.5% (20/58), respectively. This result is consistent with prior reports that were conducted in patients with NSCLC (9-11) or AGC (12). Nishino *et al.* reviewed patients who had received erlotinib in a phase II clinical trial. Although the number of target lesions according to RECIST 1.1 decreased in 51.2% of patients (22/43), 93% of patients (40/43) showed the same results in the best tumor responses between two RECIST versions (κ=0.905). In other study of Korean NSCLC patients who received epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, the ORRs according to RECIST 1.0 and RECIST 1.1 were 35.6% and 38.5%, respectively, and only 6% of patients (6/104) showed disagreement in the tumor response assessment between two RECIST versions (9). Especially in the study of AGC by Fuse *et al.*, the ORRs were 52% according to RECIST 1.0 and 55% according to RECIST 1.1, respectively.

In our study, only three patients showed disagreement of the best response between two RECIST versions. One patient with PR based on RECIST 1.0 was reclassified as SD by RECIST 1.1 because of 4 LN target lesions excluded by the new LN criteria of RECIST 1.1. Of two patients with SD by RECIST 1.0, one was downgraded to PD and the other was upgraded to PR by RECIST 1.1 with the new criteria of up to two lesions per organ. As patients showing PR or SD practically stay on the same therapy, patients with disagreement between PR and SD have no significant clinical impact of RECIST 1.1. In our study, only one patient showed disagreement of PD *vs.* SD, which would have impacted clinical decisions. Therefore, the clinical impact of RECIST 1.1 on changing therapeutic decisions seemed to be minimal.

In the present study, we did not incorporate PET scan in the evaluation of tumor response. PET scan has an important role in the assessment of tumor response using RECIST 1.1. The recent development of new target agents that induce necrosis in tumors but do not necessarily reduce the tumor size highlighted the limitations of using exclusively anatomic criteria. The RECIST Working Group acknowledged this limitation of RECIST 1.0 and included PET in RECIST 1.1. RECIST 1.1 specified that a positive finding at follow-up test after a negative finding at baseline PET should be considered as a new lesion and evidence of PD. Furthermore a positive finding at follow-up PET in patients who did not undergo PET at baseline should also be considered as a new lesion, indicating evidence of PD if the lesion was not seen at baseline CT but confirmed at follow-up CT (13). New lesions detected on PET may change the best tumor response from SD according to RECIST 1.0 to PD according to RECIST 1.1, which may lead to a lower concordance rate for tumor responses between two REICST versions. In the current study, however, no patients underwent PET scan because this test was not required in protocols at the time of clinical trials. Prospective studies with periodic PET scans are needed to evaluate its impact on the RECIST revision.

In conclusion, RECIST 1.1, despite the decreased number of target lesions and sum of tumor diameters, provided almost perfect agreement with RECIST 1.0 in the CT evaluation of tumor response of patients with AGC.

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Research Paper

Comparison of RECIST 1.0 and RECIST 1.1 in Patients with Metastatic Cancer: A Pooled Analysis

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Abstract

Background: We conducted this pooled analysis to investigate the impact of RECIST 1.1 on the selection of target lesions and classification of tumor response, in comparison with RECIST 1.0.

Methods: We searched MEDLINE and EMBASE for articles with terms of RECIST 1.0 or RECIST 1.1. We looked into all abstracts and virtual meeting presentations from the conferences of ASCO and ESMO between 2009 and 2013.

Results: There were six articles in the literature comparing the clinical impacts of RECIST 1.0 and RECIST 1.1 in patients with metastatic cancer. A total of 359 patients were recruited from the six trials; 217 with non-small cell lung cancer, 61 with gastric cancer, 58 with colorectal cancer, and 23 with thyroid cancer. The number of target lesions by RECIST 1.1 was significantly lower than that by RECIST 1.0 ($P<0.001$). Because of new lymph node criteria, fourteen patients (3.1%) had no target lesions when adopting RECIST 1.1. RECIST 1.1 showed high concordance with RECIST 1.0 in the assessment of tumor responses ($k = 0.903$). Sixteen patients (4.8%) showed disagreement between the two criteria.

Conclusion: This pooled study demonstrated that RECIST 1.1 showed a highly concordant response assessment with RECIST 1.0 in patients with metastatic cancer.

Key words: RECIST 1.0; RECIST 1.1; Target lesion; Tumor response

Introduction

The decision on subsequent cancer treatments usually depends on radiologic changes in the tumor burden, so the accurate assessment of objective therapeutic response is essential for patients receiving anti-cancer treatments. Since the World Health Organization (WHO) issued objective response criteria in 1979, the WHO guidelines have been used as the standard method for evaluating tumor response [1]. Tumor sizes are measured bi-dimensionally by the product of the longest diameter and its longest perpendicular diameter for each tumor, and tumor responses are expressed as percentage changes in the sum of tumor measurements from baseline. Because the methods for selecting and measuring target le-

sions were not clearly described in the WHO guidelines, however, the assessment of tumor response has been poorly reproducible between investigators [2,3]. In clinical practice, measuring with two dimensions and then calculating the sums of their products not only are laborious but also has a potential risk of errors. Theoretically, the simple sum of the maximum diameters of target lesions is more linearly related to cells killed than the sum of the bi-dimensional products [4]. Furthermore, the recent development of new classes of anti-cancer agents and new imaging technologies have necessitated a new methodology for evaluating tumor response [5,6].

In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) Working Group introduced a new set of tumor response criteria, the RECIST guidelines version 1.0 (RECIST 1.0) [7]. RECIST 1.0 adopted uni-dimensional measurement, instead of the bi-dimensional criterion in the WHO guidelines. Other important features of RECIST 1.0 included definition of minimum size of measurable lesion by computed tomography (CT) and instruction on how many lesions to be evaluated (up to ten, with a maximum of five per organ). RECIST 1.0 had been widely accepted as the standardized method for tumor response assessment, particularly in oncologic trials with primary end point of objective response or time to progression. However, a number of questions and issues were raised, which included the number of target lesions and the size of lymph nodes (LNs) to be measured. Subsequent rapid innovation of new imaging technologies, such as multi-detector computed tomography (MDCT) and positron emission tomography (PET), requested an update of RECIST 1.0 [8].

In 2009, the RECIST Working Group published a revised version of RECIST guidelines (RECIST 1.1) [9], which was based partly on the analyses of the database of about 6,500 patients with more than 18,000 target lesions from 16 clinical trials [10-12]. The most important changes in RECIST 1.1 include reduction in the maximum number of target lesions (up to five in total, with two per organ), new criteria for LN measurement, augmented definition of progressive disease (PD), new criteria for selecting bone lesions and cysts as target lesions, and the inclusion of PET findings for assessing tumor response (Table 1) [9,13-15].

With the expectation of improving feasibility through a more convenient and accurate assessment of both tumor response and time to progression, investigators have started to adopt RECIST 1.1 in clinical trials. Since being introduced into clinical practice, RECIST 1.1 have shown high concordance with RECIST 1.0 in the assessment of tumor responses for patients with advanced or metastatic non-small cell lung cancer (NSCLC) [16-18], gastric cancer (AGC) [19], colorectal cancer (CRC) [20], and thyroid cancer (TC) [21]. However, each study had a small number of patients with a single type of primary cancer, so it is still necessary to reveal how RECIST 1.1 affects the selection and measurement of target lesions and assessment of tumor responses in patients with metastatic cancer.

We conducted this pooled analysis to investigate the impact of RECIST 1.1 on the selection of target lesions and classification of tumor response, in comparison with RECIST 1.0.

Table 1. Summary of the major changes between RECIST 1.0 and RECIST 1.1 [15]

	RECIST 1.1	RECIST 1.0
Number of target lesions	Up to 2 per organ; up to 5 in total	Up to 5 per organ; up to 10 in total
Minimum size of target lesions	10 mm when slice thickness of CT is ≤5 mm, or 2x slice thickness when it slice thickness is ≥5 mm	10 mm (spiral CT) or 20 mm (non-spiral CT)
Assessment of lymph nodes	Short-axis measurements should be used; ≥15 mm for target ≥10 mm to < 15 mm for non-target < 10 mm for non-pathological Lymph node <10 mm in shot axis is CR	10 mm in long axis for target
CR of lymph nodes	May be used as target lesions (special notes)	Not specified
Bone lesions and cysts	5 mm absolute increase is required	Non-measurable (no specification)
PD of target lesions	Increase of non-target lesions is PD only if the increase is representative of substantial change in tumor burden	No minimum absolute size increase is required
PD of non-target lesions	Included only in the detection of new lesions	Increase in size of one or a few non-target lesions is regarded as PD, even when target lesions are stable or responding.
PET scan		Not included

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CT, computed tomography; CR, complete response; PD, progressive disease; PET, positron emission tomography

Materials and methods

Searching strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 5 of 12, May 2014), MEDLINE (from 2009 to May week 4, 2014) and EMBASE (from 2009 to week 20, 2014) for articles that included the following terms in their titles, abstracts, or keywords; 'RECIST 1.0 or RECIST 1.1', 'comparison', 'target lesion' and 'tumor response'. In addition, we surveyed all the references of relevant articles and reviews and used the 'related articles' feature in PubMed to identify the related articles. We also searched all abstracts and virtual meeting presentations from the conferences of the American Society of Clinical Oncology and European Society for Medical Oncology held between 2009 and 2013.

We thoroughly looked into all potentially eligible studies which were indentified via the above searching strategy. Clinical studies comparing the assessment of tumor response using RECIST 1.0 and RECIST 1.1 in patients who were treated with cytotoxic agents or target agents were included in the meta-analysis.

Statistical analyses

A paired Student's t test was used to assess the statistical significance of changes in the number of target lesions between RECIST 1.0 and RECIST 1.1. Chi-square test was used to compare the overall response rates (ORRs) between two groups. P-values less than 0.05 were considered significant. The level of concordance of the best tumor responses between two criteria was assessed using kappa statistics. A kappa value of more than 0.75 was interpreted as showing excellent agreement.

Results

Eligible studies

There were seven articles [16-22] and one abstract [23] in the literature comparing the clinical impacts of RECIST 1.0 and RECIST 1.1 in patients with solid tumors. However, the abstract [23] and one article [22] compared the two criteria mainly focused on the measurement of the LNs, with little information about concordance of tumor responses. Finally, six studies [16-21] that investigated the concordance of tumor responses between RECIST 1.0 and RECIST 1.1 were selected.

Patients' characteristics

A total of 359 patients with metastatic cancer were recruited from the six trials; 217 with NSCLC [16-18], 61 with GC [19], 58 with CRC [20], and 23 with TC [21]. The characteristics and clinical features of the patients were briefly described in Table 2. However, two trials by Sun *et al.* [16] and Nishino *et al.* [17] had no enough basic information about the enrolled patients.

Most patients (97.2%) had at least one target lesion according to RECIST 1.0. However, 11 patients (3.1%) had no target lesions when RECIST 1.1 was used. The most common metastatic site with measurable target lesions in patients with GC or CRC was the LNs, followed by the liver.

Patients with metastatic NSCLC were all treated with epidermal growth factor tyrosine kinase inhibitors (EGFR-TKI) such as gefitinib and elrotinib. Patients with metastatic GC or CRC received a first-line chemotherapy, most commonly with FOLFOX (5-fluorouracil/leucovorin plus oxaliplatin). Patients with radioactive iodine-refractory TC were treated with sorafenib, an oral, small molecule TKI.

Number of target lesions

The data about the number of target lesions was available in five studies [17-21], except for the trial by Sun *et al.* Especially for the two studies [19,20], we also used the raw data because the studies had been conducted in our institution (Hallym University Medical Center). The number of target lesions according to RECIST 1.1 was significantly lower than that according to RECIST 1.0 ($P < 0.001$, paired Student's *t*-test). The median number of target lesions was 3 (range, 0-10) by RECIST 1.0 and 2 (range, 0-5) by RECIST 1.1, respectively. Among 255 patients from the 5 studies, 157 (61.6%) showed a decrease in the number of target lesions when RECIST 1.1 was used. In 49 patients (21.8%), the decreased total number of target lesions was resulted from the reduced maximum number of target lesion per organ in RECIST 1.1. Twenty-six patients (11.6%) showed a decrease in the number of target lesions due to both the new LN criteria and the reduction of maximum target lesions. The new LN criteria of RECIST 1.1 contributed to the reduction of target lesions in 82 patients (32.2%). Among 359 patients, 14 (3.1%) had no target lesions when adopting RECIST 1.1, because all their target lesions were LNs < 15 mm along the short axis.

Re-categorization of LNs by RECIST 1.1

The data about re-categorization of LNs by RECIST 1.1 that were candidate target lesions based on RECIST 1.0 was only described in the study of metastatic CRC by Jang *et al.* [20]. From 58 patients, a total of 95 LNs were regarded as target lesions according to RECIST 1.0. According to RECIST 1.1, however, only 40% of the LNs were classified as target lesions.

Table 2. Summary of the 6 studies comparing RECIST 1.0 and RECIST 1.1

Characteristics	Sun *et al.* [16] NSCLC (n=104)	Nishino *et al.* [17] NSCLC (n=43)	Nishino *et al.* [18] NSCLC (n=70)	Jang *et al.* [19] GC (n=61)	Jang *et al.* [20] CRC (n=58)	Ruan *et al.* [21] TC (n=23)
	no. of pts	no. of pts	no. of pts	no. of pts	no. of pts	no. of pts
Age, years (range)	na	na	median 62 (35-84)	median 58 (26-78)	median 62 (42-79)	mean 54 (33-75)
Gender	na	na				
Male			12 (17.1%)	42 (68.9%)	29 (50%)	14 (60.9%)
Female			58 (82.9%)	19 (31.1%)	29 (50%)	9 (39.1%)
Histology	na	na				
Adenocarcinoma			63 (90%)	61 (100%)	58 (100%)	-
Well/moderately differentiated			na	22 (36.1%)	35 (60.3%)	-
Poorly differentiated			na	39 (63.9%)	23 (39.7%)	-
Non-adneocarcinoma			7 (10%)	0	0	-
Papillary			-	-	-	22 (95.6%)
Follicular			-	-	-	1 (4.4%)
Target lesions by RECIST 1.0	104 (100%)	43 (100%)	69 (98.6%)	61 (100%)	58 (100%)	14 (60.9%)
Lungs	na	na	na	2 (3.2%)	8 (13.8%)	0
Lymph nodes	na	na	na	51 (83.6%)	37 (63.8%)	0
Liver	na	na	na	8 (13.1%)	27 (46.5%)	0
Adrenal glands	na	na	na	0	2 (3.4%)	0
Ovary	na	na	na	0	3 (5.2%)	0
Median target lesions*(range)	na	2 (1-9)	2 (1-10)	3 (1-10)	4 (1-10)	3 (1-6)
No target lesion by RECIST 1.1	0	3 (6.9%)	2 (2.9%)	3 (4.9%)	6 (10.3%)	0
PET	0	6 (4.3%)	10 (14.3%)	0	0	5 (21.7%)
Treatment						
Erlotinib	36 (34.6%)	43 (100%)	63 (90%)	0	0	0
Gefitinib	68 (65.4%)	0	7 (10%)	0	0	0
Capecitabine + cisplatin	0	0	0	21 (34.4%)	0	0
FOLFOX	0	0	0	40 (65.6%)	53 (91.4%)	0
FOLFIRI	0	0	0	0	5 (8.6%)	0
Sorafenib	0	0	0	0	0	23 (100%)

Abbreviations: NSCLC, non-small cell lung cancer; GC, gastric cancer; CRC, colorectal cancer; TC, thyroid cancer; na, not available; no. of pts, number of patients; PET, positron emission tomography; FOLFOX, oxaliplatin plus 5-fluououracil/leucovorin; FOLFIRI, Irinotecan plus 5-fluorouracil/leucovorin.
* according to RECIST 1.0.

Tumor responses

We compared the tumor responses between the two criteria using 332 patients who had at least one target lesion based on RECIST 1.1. The remaining 27 patients were excluded from the comparison because they had no target lesions according to RECIST 1.1 and the tumor responses were uncertain in most of them. The results are presented in Table 3. There was high concordance between RECIST 1.0 and RECIST 1.1 in the assessment of tumor responses. The estimated kappa value was 0.903, with 95% confidence interval of 0.863-0.943. When we compared the ORRs, which were estimated regardless of the primary site and anti-cancer treatment, were not significantly different between the two criteria (42.2% by RECIST 1.1 versus 39.1% by RECIST 1.0, P=0.430).

A total of 16 patients (4.8%) showed disagreement between the two criteria. The details of the patients showing disagreement between RECIST 1.0 and RECIST 1.1 were described according to reference in Table 4. The discrepancies of the two criteria were between PR and SD in 8 patients, SD and PD in 6, and PR and CR in 2. No patients showed disagreement between PR and PD. The most common cause of the discordance was the new LN criteria, which led to the different response classification in 9 (56.3%). Four patients (25.0%) showed disagreement between the two criteria because of the maximum of target lesions (5 in total, with up to 2 lesions per organ) in RECIST 1.1. Two patients with SD according to RECIST 1.0 were reclassified as PD because of the new lesions noted on PET/CT.

Table 3. Comparison of tumor responses by RECIST 1.0 versus RECIST 1.1

Tumor response by RECIST 1.0	Tumor response by RECIST 1.1				
	CR	PR	SD	PD	Total
CR	1	0	0	0	1
PR	2	125	2	0	129
SD	0	12	111	4	127
PD	0	0	3	72	75
Total	3	137	116	76	332

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease
The level of concordance of tumor responses between RECISI 1.1 and RECIST 1.0 is 0.903 (95% CI, 0.863-0.943).
The overall response rates were not significantly different between the two criteria (42.2% by RECIST 1.1 versus 39.1% by RECIST 1.0, P=0.430)

Table 4. Summary of the patients showing disagreement between RECIST 1.0 and RECIST 1.1

Reference	Tumor type	Tumor response		No. of patients	Causes of disagreement
		RECIST 1.0	RECIST 1.1		
Sun *et al.* [16]	NSCLC	PR	CR	2	LNs < 10 mm
		SD	PR	3	Equivocal LNs
		SD	PD	1	A definitely increased LN
Nishino *et al.* [17]	NSCLC	SD	PD	2	New lesions on PET
		PD	SD	1	A single LN < 10mm
Nishino *et al.* [18]	NSCLC	SD	PR	1	Decreased number of target lesion
Jang *et al.* [19]	GC	PR	SD	1	Four LNs < 15 mm
		SD	PR	1	Up to 2 target lesion per organ
		SD	PD	1	Up to 2 target lesion per organ
Jang *et al.* [20]	CRC	PR	SD	1	Two LNs < 15 mm
		PD	SD	1	Up to 2 target lesion per organ
		PD	SD	1	An absolute size increase of at least 5 mm
Ruan *et al.* [21]	TC	SD	PR	1	Not described

Discussion

Since RECIST 1.1 was presented in 2009 [9], the impact of RECIST 1.1 has been compared with RECIST 1.0 in patients with metastatic NSCLC [16-18], AGC [19], CRC [20], and TC [21]. However, each study had a small number of patients with a single type of primary cancer. In this pooled study, we investigated the impact of RECIST 1.1 on the selection of target lesions and assessment of the best tumor responses. RECIST 1.1 significantly decreased the number of target lesions to be measured in patients with metastatic cancer. However, there was an excellent agreement in the assessment of tumor responses between RECIST 1.0 and RECIST 1.1.

As expected, RECIST 1.1 affected the number of target lesions. The maximum number of target lesions to be assessed in RECIST 1.1 is reduced from 10 to 5 in total, and from 5 to 2 per organ. While the total of 10 target lesions in RECIST 1.0 was arbitrarily selected, RECIST 1.1 defined a total of 5 lesions through the patients' data analysis [10] and statistical simulating studies [11,14]. Out of 255 patient from 5 studies in which the number of target lesions were described [17-21], 157 (61.6%) showed a decrease in the number of target lesions when RECIST 1.1 was adopted. In 49 patients (21.8%), the criteria of two lesions per organ contributed to the decreased number of target lesions. According to RECIST 1.1, lytic or mixed lytic-blastic bone lesions with an identifiable soft tissue component may be used as target lesions. In this pooled analysis with 359 patients, however, only one with TC newly had a bone target lesion when adopting RECIST 1.1.

RECIST 1.1 recommends the measurement of LN along its short axis, regarding LNs of at least 15 mm as target lesions. LN with at least 10 mm but less than 15 mm in its short axis, even though it may be pathological, is considered non-target lesion, and LN with a short axis of less than 10 mm is regarded as normal. These changes in the LN evaluation criteria also had a considerable impact on the number of target lesions. In this meta-analysis, the new LN criteria of RECIST 1.1 led to the reduction of target lesions in 82 patients (32.2%), including 26 (11.6%) in whom the decrease was attributable to both the new LN criteria and the reduction of maximum target lesions.

From the RECIST data warehouse, 90.5% of LNs were regarded as target lesion according to the new LN criteria of RECIST 1.1 [13]. In the study of patients with GC by Jang *et al.*, however, among 95 LNs considered to be target lesions by RECIST 1.0, only 38 (40 %) were defined as target lesions based on RECIST 1.1 [20]. These results are in agreement with those of the study conducted by Fuse *at al.* in patients with metastatic GC. Out of 172 LNs regarded as target lesions by RECIST 1.0, only 66 (38%) were defined as target lesions based on RECIST 1.1 [22]. Piatek *et al.* found the similar results in patients with prostate cancer. Among 158 LNs regarded as target lesions by RECIST 1.0, only 66 (41.8%) satisfied the LN criteria of RECIST 1.1 [23]. Therefore, the new LN criteria of RECIST 1.1 may alter the eligibility of patients for clinical trials in which the ORR or time to progression is a primary endpoint. In the study by Fuse *et al.* the proportion of patients with target lesions was significantly decreased from 67% to 53% by adopting RECIST 1.1 [22]. In this meta-analysis, 14 patients (3.1%) no longer had target lesions when adopting RECIST 1.1, because all their target lesions were LNs < 15 mm along the short axis. If studies using RECIST 1.1 had been planned, these patients would have been excluded from clinical trials. RECIST 1.1 with more stringent LN measurement rules, however, may categorize more patients as CR than RECIST 1.0. In the study by Sun *et al.*, two NSCLC patients with PR according to RECIST 1.0 were re-categorized as CR because LNs with short axes of < 10 mm were considered normal based on RECIST 1.1 [16].

This pooled study demonstrates that there is high concordance between RECIST 1.0 and RECIST 1.1 in the assessment of tumor responses. When comparing the tumor response assessment in 332 patients who had at least one target lesion based on RECIST 1.1, the level of agreement in tumor responses between the two criteria was very high, with a kappa value of 0.903. The ORRs estimated regardless of the primary site and anti-cancer treatment were not significantly different between the two criteria (42.2% by RECIST 1.1 versus 39.1% by RECIST 1.0, P=0.430). The disagreement between the two RECIST versions was observed in 16 patients (4.8%). The most common cause of the discordance was the new LN criteria (9 patients), followed by the maximum of target lesions in RECIST 1.1 (6 patients). As patients who achieve PR or SD practically stay on the same treatment, patients showing discordance between PR and SD would have no significant clinical impact of RECIST 1.1. In this study, only six patients (1.8%) displayed disagreement between SD and PD. Therefore, the clinical impact of RECIST 1.1 on changing therapeutic decisions seemed to be minimal.

Several limitations of this pooled analysis should be noted. First, PET was not routinely performed in all 6 studies. PET scans have an important role in the assessment of tumor response using RECIST 1.1. New lesions detected on PET scans change the tumor response from PR or SD according to RECIST 1.0 to PD according to RECIST 1.1. Therefore, the incorporation of PET may have a significant influence on the assessment of tumor responses based on RECIST 1.1. In this pooled analysis, only 21 patients (5.8%) underwent PET. Two patients had new lesions on PET scans, which changed the tumor response from SD to PD. One patient with NSCLC did not undergo baseline PET, and a new lesion was detected on PET scans during therapy. The new lesion was confirmed by the follow-up CT. If the studies had performed PET more frequently, the newly detected lesions could have led to a lower concordance rate for tumor responses between the two RECIST versions. Second, the comparison of tumor responses between the two criteria was conducted only in patients with at least one target lesion according to RECIST 1.1. According to RECIST 1.0, the increase in size of one or a few non-target lesions was regarded as PD, even though target lesions are stable or responding. Based on RECIST 1.1, however, patients with PR or SD based on target lesion response are categorized as PD, only if the increase of non-target lesions is representative of substantial change in tumor burden. Therefore, if the comparison had included patients with non-target lesion, the new criteria of non-target lesion would have affected the concordance between RECIST 1.0 and RECIST 1.1. Third, this pooled analysis only contains patients with four types of primary tumors (NSCLC, GC, CRC, and TC). This means that the results may be insufficient to be generalized for patients with other primary cancer.

In conclusion, this pooled study demonstrates that RECIST 1.1 provides a highly concordant response assessment with RECIST 1.0 in patients with metastatic cancer. Because of the more stringent LN criteria, however, RECIST 1.1 may adversely affect the patients' eligibility for clinical trials.

Conflict of Interest

Authors do not have any conflict of interest.

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

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PROTOCOLE ACCORD 11/0402

N° EudraCT 2004-001985-42

ETUDE RANDOMISEE DE PHASE II / III COMPARANT L'ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] A LA GEMCITABINE EN PREMIERE LIGNE DE CHIMIOTHERAPIE DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Essai OXIPAN

Version n°9 contenant les amendements n°1, 2, 3, 5, 7, 8, 9 et 10 approuvée par le CPP EST-III Le 07/05/2009

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APPROBATION ET SIGNATAIRES DU PROTOCOLE ACCORD 11/0402 CONTENANT LES AMENDEMENTS N°1, 2, 3, 5, 7, 8, 9 et 10

N° EudraCT 2004-001985-42

ETUDE RANDOMISEE DE PHASE II / III COMPARANT L'ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] A LA GEMCITABINE EN PREMIERE LIGNE DE CHIMIOTHERAPIE DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

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Je reconnais avoir pris connaissance de l'ensemble du protocole ACCORD 11/0402 et je m'engage à conduire ce protocole conformément aux Bonnes Pratiques Cliniques, à la Loi Huriet et tel qu'il est décrit dans ce document.

J'assume les responsabilités qui m'incombent en tant qu'investigateur principal et dont notamment :

- le recueil du consentement éclairé, daté et signé par les patients avant toute procédure de sélection dans le protocole,
- la validation des cahiers d'observation complétés pour chacun des patients inclus dans l'étude,
- l'accès direct aux documents-source pour les vérifications effectuées par l'attaché de recherche clinique (ARC) mandaté par le promoteur,
- l'archivage des documents essentiels de l'étude pendant une durée de 15 ans.

INVESTIGATEUR PRINCIPAL DE L'ETABLISSEMENT CONCERNE :

Nom et adresse de l'établissement :

Nom de l'investigateur principal :

Date : Signature :

SYNOPSIS – PROTOCOLE ACCORD 11/0402

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TITRE	Etude randomisée de phase II / III comparant l'association Folfirinox [oxaliplatine / irinotecan / LV5FU] à la gemcitabine en première ligne de chimiothérapie de patients atteints d'un cancer du pancréas métastatique.
PATHOLOGIE	Adénocarcinomes pancréatiques métastatiques
OBJECTIFS	**Objectif principal de la phase II** : ▪ Comparer les taux de réponse objective entre les 2 bras de traitement. **Objectif principal de la phase III** : ▪ Comparer la survie **Objectif secondaire de la phase II** : ▪ Comparer la toxicité de ces traitements. **Objectifs secondaires de la phase III** : ▪ Comparer la survie sans progression dans les 2 bras. ▪ Comparer la qualité de vie dans les 2 bras. ▪ Comparer le taux de réponse ▪ Comparer la toxicité de ces traitements
METHODOLOGIE	Etude randomisée de phase II / III comparant l'association Folfirinox [oxaliplatine / irinotecan / LV5FU] à la gemcitabine en première ligne de chimiothérapie de patients atteints d'un cancer du pancréas métastatique.
CRITERES D'INCLUSION	▪ Adénocarcinome du pancréas histologiquement ou cytologiquement prouvé, ▪ Maladie métastatique, ▪ Maladie mesurable en dehors d'un territoire irradié, ▪ Une lésion est mesurable si elle peut être mesurée avec précision dans au moins une dimension (le plus grand diamètre étant reporté) soit > à 20 mm avec un scanner conventionnel, soit > à 10 mm avec un scanner spiralé. ▪ Absence de chimiothérapie antérieure, ▪ Absence de radiothérapie abdominale antérieure (à l'exception d'une radiothérapie antalgique si elle n'a pas été effectuée sur les cibles mesurables), ▪ Age compris entre 18 et 75 ans inclus, ▪ Etat général : OMS 0-1, ▪ Fonction hématologique satisfaisante (PNN ≥ 1500/mm3, plaquettes ≥ 100 000/mm3), ▪ Fonction hépatique satisfaisante (bilirubine ≤ 1,5 fois la limite supérieure de la normale (un drainage biliaire est autorisé)), ▪ Fonction rénale satisfaisante: créatininémie < 120 µmol/L, soit 13.6 mg/L, ▪ Absence d'insuffisance cardiaque ou d'angine de poitrine non médicalement controlée ou d'infarctus dans les 12 mois précédents l'inclusion, ▪ Information du patient et signature du consentement éclairé.

CRITERES DE NON INCLUSION	▪ Autres types de tumeurs du pancréas, en particulier tumeur endocrine ou à cellules acineuses, ▪ Présence de métastases cérébrales ou méningées, ▪ Contre-indications spécifiques au traitement étudié, ▪ Antécédents de diarrhée chronique ou de maladie inflammatoire du côlon ou du rectum, ou d'occlusion ou de sub-occlusion non résolues sous traitement symptomatique, ▪ Infection évolutive active ou autre pathologie grave sous-jacente susceptible d'empêcher le patient de recevoir le traitement, ▪ Autre cancer concomitant ou antécédent de cancer en dehors d'un cancer in situ du col utérin ou d'un épithélioma baso ou spinocellulaire, ▪ Patient déjà inclus dans un autre essai thérapeutique avec une molécule expérimentale, ▪ Femme enceinte, susceptible de l'être ou en cours d'allaitement, ▪ Personnes privées de liberté ou sous tutelle, ▪ Impossibilité de se soumettre au suivi médical de l'essai pour des raisons géographiques, sociales ou psychiques.
DESCRIPTION SUCCINTE DES PRODUITS ET DEROULEMENT DU TRAITEMENT	**Bras A : Folfirinox** - Oxaliplatine 85 mg/m^2 IV en perfusion de 2 heures, - Irinotecan 180 mg/m^2 IV en perfusion de 90mn. - Acide folinique 400 mg/m^2 IV en perfusion de 2 heures - 5-FU bolus 400 mg/m^2 IV en 5 minutes. - 5-FU continu 2,4 g/m^2 IV en perfusion continue sur 46 heures. Reprise de cycle à J15. **Bras B : gemcitabine** - Gemcitabine 1000 mg/m^2 à J1, J8, J15, J22, J29, J36, J43. Reprise à J57 et poursuite du traitement 3 semaines sur 4.
CRITERES D'EVALUATION	**Pour la phase II** **L'efficacité** Critère principal : taux de réponses objectives (RECIST). Critère secondaire : Toxicités de grade 3-4 **Pour la phase III** Critère principal : la survie Critères secondaires : Qualité de vie (échelle EORTC QLQ-C30 version 3.0 tous les 14 jours). Toxicités selon l'échelle NCI-CTC version 3.0 Survie sans progression, taux de réponse
NOMBRE DE PATIENTS NECESSAIRES	**Pour la Phase II** : Les patients seront inclus en 3 paliers avec à chaque étape une évaluation du taux de réponse dans le bras A (Folfirinox) Paliers : 1er / 2e / 3e **N** : 20 / 30 / 40 **R** : 2 / 4 / 6 **A** : 8 / 11 / - **N** = nombre de patients prévus dans le bras A Folfirinox **R** = nombre de patients ayant répondu au Folfirinox **A** = nombre de patients ayant répondu au-delà duquel la phase II est interrompue. On passe alors directement en Phase III car on considère que le Folfirinox donne au moins 20% de réponses objectives. ◆ A la fin de la 1ère étape (20 malades inclus) : - si l'on a observé 2 réponses objectives (RO) ou moins, on arrêtera

	l'essai en concluant que le Folfirinox n'est pas efficace. - si l'on a observé 8 réponses objectives ou plus, on passera en phase III. - si l'on a observé entre 3 et 7 réponses objectives, on continuera la phase II : inclusion de 10 malades supplémentaires. ◆ A la fin de la 2ème étape (30 malades en tout) : - si l'on a observé 4 réponses objectives ou moins, on conclura que le Folfirinox n'est pas efficace. - si l'on a observé 11 réponses objectives ou plus, on conclura que le Folfirinox est efficace et on passera à la phase III. - si l'on a observé entre 5 et 10 réponses objectives, on continuera la phase II : inclusion de 10 malades supplémentaires. ◆ A la fin de la 3ème étape (40 malades en tout) : - si l'on a observé 6 réponses objectives ou moins, on conclura que le Folfirinox n'est pas suffisamment efficace, on ne passe donc pas en phase III. - si l'on a observé 12 réponses objectives ou plus, on conclura que le traitement est efficace et on passera à la phase III - Entre 7 et 11, on ne peut pas conclure et on passe à la phase III pour avoir plus de patients. Si nous considérons que 10 % des patients seront inévaluables, pour la réponse, il est donc nécessaire d'inclure **un total de 88 patients** répartis en **2 groupes** équivalents de **44 patients** sur une période de 2 ans **Pour la phase III :** Pour mettre en évidence une différence dans les médianes de survie de 3 mois (passage de 7 à 10 mois de médiane), soit un risque relatif de 0.70, il faudra inclure **360 patients** pour maintenir un risque global alpha de 5 %, en acceptant un risque beta de 20 % (puissance de l'essai = 80%). Cette puissance sera obtenue lorsque **250** événements auront été observés (calcul effectué avec le logiciel East 5). Les patients inclus dans la phase II seront pris en compte pour l'étude de phase III.
NOMBRE DE CENTRES ESTIMES	15 centres pour la phase II 50 centres pour la phase III
DUREE DE L'ETUDE	début des inclusions phase II : juin 2004 fin des inclusions phase II : juin 2006 début des inclusions phase III : juin 2006 fin des inclusions phase III : juin 2009 fin de l'étude : juin 2010
ANALYSE STATISTIQUE	L'analyse statistique sera effectuée sur la totalité des patients randomisés en intention de traiter. La survie globale des patients éligibles est calculée à partir de la date de randomisation, la survie sans progression (DFS) est calculée depuis la date de randomisation jusqu'à la date de rechute, les taux de survie sans progression seront estimés par la technique de Kaplan Meier et les comparaisons seront réalisées au moyen d'un test de Log-rank. Un modèle de Cox sera utilisé pour l'analyse multifactorielle, prenant en compte les facteurs pronostiques majeurs de survie en maladie métastatique (état général et plus accessoirement, l'âge, la différenciation tumorale, l'albuminémie, les LDH et les phosphatases alcalines).

TABLE DES MATIERES

1 . INTRODUCTION ET RATIONNEL DE L'ESSAI

1.1 Faut-il traiter par chimiothérapie un cancer du pancréas exocrine métastatique ?

Le cancer du pancréas métastatique reste une maladie incurable, associée à une médiane de survie de 2 à 4 mois en l'absence de chimiothérapie (1-2). Sept études ont comparé une chimiothérapie palliative à un traitement purement symptomatique (3-9). Quatre études datant des années 1980 ne montrent pas de différence de survie entre les deux groupes (3-6). Deux des 3 études les plus récentes ont montré une amélioration de la survie et de la qualité de vie en faveur du groupe recevant la chimiothérapie (7,8). Dans la première étude (7), les patients traités par chimiothérapie sont moins déprimés (échelle HADS). Dans la seconde étude (8), 38 % des patients traités par chimiothérapie ont une amélioration de leur qualité de vie (jugée par deux observateurs indépendants à partir des réponses au questionnaire EORTC QLQ-C30) pendant plus de quatre mois, contre 13 % des patients recevant un traitement symptomatique. Le groupe traité par chimiothérapie a un meilleur indice de Karnofsky, un meilleur état psychologique, et moins d'anorexie, de douleurs, de fatigue et de dyspnée.

Toutefois, les quelques études ouvertes qui ont étudié l'impact sur la régression des symptômes et la qualité de vie indiquent qu'au mieux 20 à 35 % des patients tirent bénéfice d'une chimiothérapie, le bénéfice étant habituellement de courte durée (10). En analyse multifactorielle, les facteurs pronostiques de survie en maladie métastatique sont surtout l'état général et plus accessoirement, l'âge, la différentiation tumorale, l'existence d'une anorexie, l'albuminémie, les LDH et les phosphatases alcalines (11-15-19-47-51) Une étude portant sur 3023 patients traités par gemcitabine montre également une médiane de survie particulièrement courte chez les patients dont l'indice de Karnofsky est inférieur à 70 (schématiquement équivalent à OMS 2), la médiane de survie étant de 2,4 mois et la survie sans progression de 1,7 mois (11). La décision de traiter les patients OMS 2 doit donc être prise au cas par cas.

1.2 La gemcitabine est la chimiothérapie de référence

A la suite d'une étude randomisée portant sur 126 patients (12), la gemcitabine 1000 mg/m^2 en administration hebdomadaire est considérée comme la monochimiothérapie de référence. Elle a été marginalement plus efficace que le 5-FU en bolus administré 5 jours toutes les quatre semaines. Cependant, avec la gemcitabine, seulement trois réponses partielles ont été observées parmi 56 patients présentant une maladie mesurable (5,4 %) alors qu'aucun des patients traités par 5-FU n'a répondu. La médiane de survie a été améliorée de 1,2 mois, passant de 4,4 mois pour les patients traités par 5-FU versus 5,6 mois pour les patients recevant la gemcitabine (p = 0,0025). Dans d'autres études randomisées, la gemcitabine en monothérapie est associée à une médiane de survie de 4.4 à 6.6 mois (13-17). Aucune étude randomisée n'a montré à ce jour une amélioration significative de la survie et/ou de la qualité de vie par rapport à la gemcitabine en monothérapie (17-40-41-42-44-46-47-48-49). La gemcitabine constitue actuellement le traitement de référence de la plupart des études randomisées (EORTC, FFCD, groupes coopérateurs américains).

1.3 Résultats obtenus avec le 5-FU, l'irinotecan et l'oxaliplatine

Le taux de réponse historique attribué au 5 Fluorouracile (15 % à 36 %) est très surestimé, comme le montrent 3 études randomisées récentes. Dans une étude portant sur 281 patients, le 5-FU en perfusion continue à la dose de 225 mg/m^2/j n'a amené un taux de réponse que de 1 % et une médiane de survie de 5,1 mois (18). A la dose de 300 mg/m^2/j, le taux de réponse observé chez 105 patients a été de 8,6 % et la médiane de survie de 5,1 mois (19). Dans l'étude de la FNCLCC, le taux de réponse du 5-FU en bolus était de 0 % versus 12 % pour une association de 5-FU en perfusion continue et cisplatine (20), sans avantage de survie significatif en faveur de l'association.

L'irinotecan est un médicament actif dans le cancer du pancréas, associé à des taux de réponse de 6 à 9 %, réponses d'une durée médiane de 5,7 mois avec une médiane de survie de 5,2 mois (21-22). Une efficacité en troisième ou quatrième ligne a également été décrite (45). L'oxaliplatine en monothérapie

n'est pas efficace, mais associé au 5 Fluorouracile et à l'acide folinique, un taux de réponse de 12 % a été décrit sur 28 patients. La médiane de survie était de 8,5 mois (23). Une synergie in vitro entre le SN-38, métabolite actif de l'Irinotecan, et l'oxaliplatine a été décrite (24).

Le SN-38, le métabolite principal de l'irinotecan, est plus cytotoxique sur des cultures d'adénocarcinome pancréatique que le cisplatine, la mitomycine C et le 5-FU (31). D'autres études pré-cliniques ont montré une synergie entre SN-38 et 5-FU lorsque le SN-38 précède l'exposition au 5-FU (32). D'autres études en laboratoire ont confirmé l'effet antitumoral de l'irinotecan sur des cultures de cellules tumorales pancréatiques et sur des xénogreffes de cancers du pancréas (34).

L'effet cytotoxique de l'oxaliplatine a été décrit sur trois lignées cellulaires pancréatiques différentes et sur des métastases hépatiques de cancers du pancréas (29). In vitro, la cytotoxicité est accrue lorsqu'on ajoute de l'oxaliplatine aux cultures avant ou en même temps qu'un dérivé de la camptothécine (35). Cette synergie semble liée à la stabilisation des adduits de l'oxaliplatine sur l'ADN lorsque les cellules tumorales sont exposées d'abord à l'oxaliplatine, puis à l'inhibiteur de topoisomérase. De ce fait, l'irinotecan pourrait réduire la résistance à l'oxaliplatine. En dehors de la toxicité hématologique, ces deux médicaments n'ont par ailleurs pas de toxicité croisée.

Dans l'étude de phase I de l'association Folfirinox (oxaliplatine, irinotecan, acide folinique, 5-FU en bolus, 5-FU en perfusion continue), il a été observé une réponse complète et une réponse partielle parmi cinq cas de cancers du pancréas (25).

1.4 Résultats de l'étude de phase II Folfirinox

Du fait des résultats encourageants observés en phase I, une étude de phase II de l'association Folfirinox a été mise en place dans 9 centres. Quarante-sept patients OMS 0-1, présentant une maladie localement avancée ou une maladie métastatique ont été inclus. Quarante-six patients ont été traités. Trente-quatre patients étaient en maladie métastatique et 12 présentaient une maladie localement avancée inopérable. Le nombre moyen de cures a été de 8 (1-24). La tolérance a été excellente. Sur 356 cycles, 14 % ont fait l'objet d'une réduction de dose. Quatre patients ont reçu du G-CSF. Deux épisodes de neutropénie fébrile sont survenues. Trente-cinq pour cent des patients ont présenté une neutropénie de grade 3 (15 % des cycles) et 17 % une neutropénie de grade 4 (7 % des cycles). Une diarrhée de grade 3 est survenue chez 11 patients et 3 % des cycles. Une diarrhée de grade 4 est survenue chez 2 % des patients et moins de 1 % des cycles. La neurotoxicité de l'oxaliplatine a été tolérable, avec 15 % de neuropathie de grade 3 (échelle de Lévi) et 3 % des cycles. Il n'y a pas eu de décès toxique.

En termes de taux de réponses, après relecture extérieure indépendante de tous les scanners, il a été observé deux réponses complètes, dix réponses partielles, vingt stabilisations tumorales, soit un taux de réponse de 26 % (intervalle de confiance : 13-39 %), et 61 % de contrôle tumoral. Le taux de réponse a été identique en maladie métastatique et en maladie localement avancée.

Une progression a été observée dans un délai moyen de 5,1 mois. La médiane de survie a été de 10,2 mois (9,5 mois en maladie métastatique et 15,5 mois dans les cancers localement avancés). Quarante trois pour cent des patients étaient en vie à un an. La durée moyenne de réponse objective a été de 9,3 mois (8-14 mois) et la durée moyenne de stabilité de 6,2 mois (26-27).

La qualité de vie était évaluée à l'inclusion et avant chaque cycle. La compliance au questionnaire a été de 66 %. Trente huit questionnaires sont disponibles à l'inclusion et 36 lors du dernier cycle. La comparaison entre les scores initiaux de qualité de vie et ceux du dernier cycle montre une amélioration de tous les domaines du QLQ-C30 (sauf domaine cognitif, difficultés financières et diarrhée). L'amélioration est surtout constatée chez les patients répondeurs ou stables. Une amélioration de plus de 10 points des scores est observée pour les domaines d'activités, psychologique, social, alors qu'une réduction des scores de symptômes est observée, surtout pour la douleur, l'insomnie, la perte d'appétit et la constipation. Chez les répondeurs, l'amélioration de qualité de vie globale est en moyenne de 25 points sur une échelle de 100 (soit une « grande » amélioration

selon les critères d'OSOBA (28)). Ces résultats encourageants justifient la réalisation d'une étude randomisée Folfirinox versus traitement de référence, la gemcitabine en monothérapie.

2 . OBJECTIFS DE L'ESSAI

2.1 Objectif principal de la Phase II

Evaluer l'efficacité de l'association oxaliplatine, irinotecan, 5 fluorouracile et acide folinique (Folfirinox – bras A) dans le traitement du cancer du pancréas métastatique par rapport au traitement de référence par gemcitabine (bras B), en comparant les taux de réponses objectives entre les 2 bras.

2.2 Objectifs secondaires de la Phase II

- Comparer la tolérance aux traitements, en particulier les toxicités de grade 3-4.

2.3 Objectif principal de la Phase III

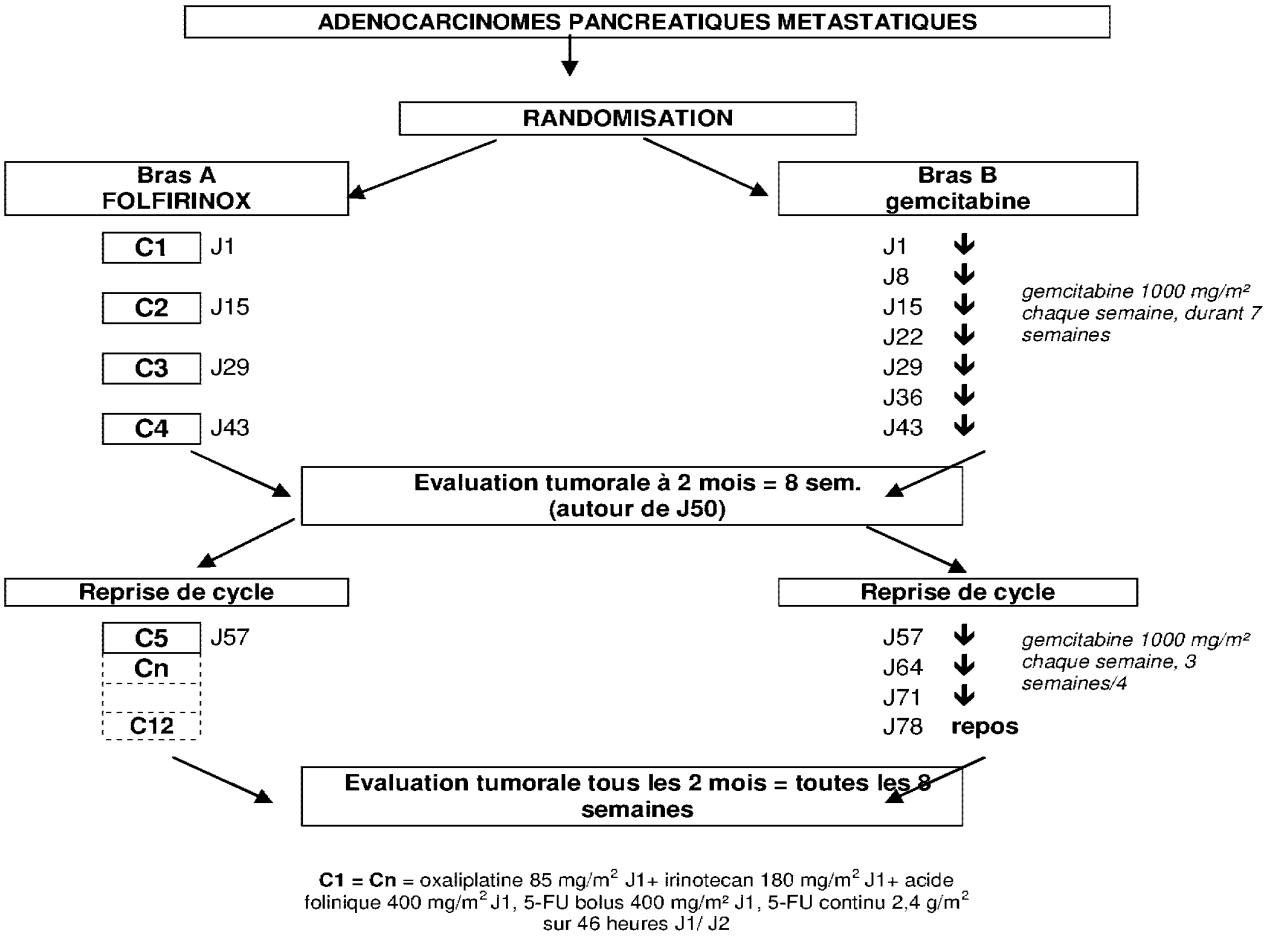
L'objectif principal est de comparer les effets sur la survie globale de deux schémas thérapeutiques, l'association Folfirinox – bras A par rapport au traitement de référence par gemcitabine bras B.

2.4 Objectifs secondaires de la Phase III

- Comparer la survie sans progression dans les 2 bras
- Comparer la qualité de vie dans les 2 bras.
- Comparer le taux de réponse
- Comparer la toxicité aux traitements.

3 . METHODOLOGIE

Essai de phase II / III avec Bénéfice Individuel Direct (BID), randomisé, ouvert, multicentrique, comparant le traitement A (Folfirinox) au traitement B (gemcitabine).



C1 = Cn = oxaliplatine 85 mg/m^2 J1+ irinotecan 180 mg/m^2 J1+ acide folinique 400 mg/m^2 J1, 5-FU bolus 400 mg/m^2 J1, 5-FU continu 2,4 g/m^2 sur 46 heures J1/ J2

Les patients seront traités pour un maximum conseillé de 6 mois.

4 . SELECTION DES PATIENTS

4.1 Critères d'inclusion

1. Adénocarcinome du pancréas histologiquement ou cytologiquement prouvé,
2. Maladie métastatique,
3. Maladie mesurable en dehors d'un territoire irradié,

   Une lésion est mesurable si elle peut être mesurée avec précision dans au moins une dimension (le plus grand diamètre étant reporté) soit > à 20 mm avec un scanner conventionnel, soit > à 10 mm avec un scanner spiralé.
4. Absence de chimiothérapie antérieure,
5. Absence de radiothérapie abdominale antérieure (à l'exception d'une radiothérapie antalgique si elle n'a pas été effectuée sur les cibles mesurables),
6. Age compris entre 18 et 75 ans inclus,
7. Etat général : OMS 0-1,
8. Fonction hématologique satisfaisante (PNN ≥ 1500/mm^3, plaquettes ≥ 100 000/mm^3),
9. Fonction hépatique satisfaisante (bilirubine ≤ 1,5 fois la limite supérieure de la normale (un drainage biliaire est autorisé)),

10. Fonction rénale satisfaisante: créatininémie < 120 µmol/L, soit 13.6 mg/L,
11. Absence d'insuffisance cardiaque ou d'angine de poitrine non médicalement controlée ou d'infarctus dans les 12 mois précédents l'inclusion,
12. Information du patient et signature du consentement éclairé.

4.2 Critères de non inclusion

1. Autres types de tumeurs du pancréas, en particulier tumeur endocrine ou à cellules acineuses,
2. Présence de métastases cérébrales ou méningées,
3. Contre-indications spécifiques au traitement étudié,
4. Antécédents de diarrhée chronique ou de maladie inflammatoire du côlon ou du rectum, ou d'occlusion ou de sub-occlusion non résolues sous traitement symptomatique,
5. Infection évolutive active ou autre pathologie grave sous-jacente susceptible d'empêcher le patient de recevoir le traitement,
6. Autre cancer concomitant ou antécédent de cancer en dehors d'un cancer in situ du col utérin ou d'un épithélioma baso ou spinocellulaire,
7. Patient déjà inclus dans un autre essai thérapeutique avec une molécule expérimentale,
8. Femme enceinte, susceptible de l'être ou en cours d'allaitement,
9. Personnes privées de liberté ou sous tutelle,
10. Impossibilité de se soumettre au suivi médical de l'essai pour des raisons géographiques, sociales ou psychiques.

5 . RANDOMISATION / ENREGISTREMENT DES PATIENTS

Après signature du formulaire de consentement et validation des résultats du bilan initial d'inclusion, les patients éligibles seront randomisés auprès du centre de randomisation de l'essai.
L'investigateur devra faxer la fiche de randomisation complétée et signée auprès du centre de gestion de la société EURAXI Pharma, Service de biométrie. En retour, le Centre de gestion des données faxera la confirmation de randomisation en précisant le bras de traitement et le numéro du patient.

Les coordonnées du centre de randomisation sont :

Gestion des Randomisations et Data-management

Sébastien LOUVEAU
EURAXI PHARMA
Service de Biométrie

du lundi au vendredi de 9h à 16h
Fax : 02.47.74.30.82 / Tél. : 02.47.74.30.47

Le tirage au sort est stratifié stratification classique sur :

- **le centre**
- **l'état général OMS (0 versus 1)**
- **localisation (tête versus autre)**

Le traitement doit débuter dans les 7 jours suivant la randomisation.

6 . TRAITEMENTS

6.1 Description des traitements à l'essai

A l'issue du tirage au sort, les sujets reçoivent soit le traitement A (FOLFIRINOX), soit le traitement B (gemcitabine) :

Traitement A: Folfirinox

- oxaliplatine (Eloxatine®)85 mg/m^2 J1 en 2h, puis
- irinotecan (Campto ®)180 mg/m^2 J1 en 90mn
- acide folinique 400 mg/m^2, J1 en 2h (pendant la perfusion d'irinotécan)
- 5-FU bolus 400 mg/m² J1 suivi de 5-FU continu 2,4 g/m^2 **au total** sur 46 heures, **soit 1,2 g/m^2 à J1 et 1,2 g/m^2 à J2.**.

Le traitement sera poursuivi jusqu'à progression et un maximum de 12 cycles est conseillé.

L'acide folinique peut être remplacé par du lévofolinate de calcium pour les centres qui le souhaitent. La dose devient alors 200mg/m^2.

Traitement B: gemcitabine

- gemcitabine 1000 mg/m^2 en 30 mn **par voie intra veineuse stricte**, à J1, J8, J15, J22, J29, J36, J43.

Reprise de la gemcitabine à J57, 3 semaines sur 4 (J57, J64, J71 suivi d'une semaine de pause).

Le traitement par gemcitabine sera poursuivi selon le même schéma (3 semaines sur 4) jusqu'à progression et un maximum de 6 mois est conseillé.

Les produits seront préparés selon les Bonnes Pratiques en Chimiothérapie et selon les modalités qui sont décrites en annexe 1.

L'irinotécan et l'oxaliplatine seront fournis par le Promoteur. Les autres produits seront pris dans le stock habituel de la pharmacie.

L'oxaliplatine et l'irinotécan seront fournis par le promoteur :

➔ ces produits seront étiquetés conformément à l'article R.5123 du Code de la Santé Publique et aux Recommandations de l'Annexe 1 des Bonnes Pratiques de Fabrication européennes.

➔ ces produits seront distribués aux différentes pharmacies des établissements de soins selon les Bonnes Pratiques de Distribution (BPD).

Une traçabilité de tous les produits utilisés dans le cadre de cette étude clinique, qui sont fournis soit par le promoteur ou soit par la pharmacie de l'établissement de soins, devra être assurée pendant toute la durée de l'étude.

6.2 Déroulement du traitement

6.2.1 Bras A : Folfirinox : association oxaliplatine + irinotecan + acide folinique + 5 fluorouracile

Le traitement débutera par l'administration d'oxaliplatine à la dose de 85 mg/m^2 IV en perfusion de 2 heures, puis sera suivi de l'administration simultanée de l'acide folinique à la dose de 400 mg/m^2 IV en perfusion de 2 heures et de l'irinotecan à la dose de 180 mg/m^2 IV en perfusion de 1H30, à débuter immédiatement après la fin de la perfusion d'oxaliplatine.
Le 5-FU sera administré immédiatement après la fin de la perfusion d'acide folinique et consistera en une dose de 400 mg/m^2 en bolus IV 5 minutes, puis en une perfusion continue sur 46 heures de 2,4 g/m^2.

Le cycle sera administré toutes les 2 semaines. Le traitement peut se faire en hôpital de jour.

Le traitement sera poursuivi jusqu'à rechute et un maximum de 12 cures est conseillé

6.2.2 Bras B : gemcitabine

L'administration de la gemcitabine se fera à la dose de 1000mg/m^2, en 30mn par intraveineuse stricte.

L'administration doit être répétée **une fois par semaine pendant 7 semaines suivie de 14 jours de repos**. Puis, à partir du cycle suivant, l'administration doit être répétée une fois par semaine pendant **3 semaines consécutives, suivie d'une semaine de repos**. Les doses pourront être réduites avant chaque administration de la chimiothérapie, en fonction de la tolérance individuelle des patients à la gemcitabine.

6.2.3 Durée du traitement (pour les deux bras)

Il est conseillé 6 mois de chimiothérapie. Au delà de cette période de traitement protocolaire, la prise en charge médicamenteuse ou non du patient, est laissé au libre choix de l'investigateur.

De même en cas de progression, la prise en charge thérapeutique du patient est laissé au choix de l'investigateur.

6.3 Adaptation des doses

En cas de réduction de doses nécessaire, les posologies réduites seront maintenues ultérieurement.
Toute toxicité de grade 4 récurrente à l'identique malgré une diminution de doses, amène le patient à arrêter le traitement.

LES PATIENTS NE SORTENT JAMAIS DE L'ETUDE.
ILS SONT SUIVIS JUSQU'AU DECES.

6.3.1 Toxicité hématologique

6.3.1.1 Selon le bilan biologique à J15

TRAITEMENT A : Folfirinox

NFS à J15	RETARD DE CYCLE	RÉDUCTION DE DOSE		
		Irinotecan (CPT-11)	**Oxaliplatine (L-OHP)**	**LV5FU**
PNN ≥ 1.5 x 10^9 /l et plaq ≥ 75x10^9 /l	Pas de retard de cycle	Pas de réduction de dose		
PNN < 1.5 x 10^9 /l	Retarder le traitement jusqu'à PNN ≥ 1500 (jusqu'à J22 ou J29 si nécessaire). En cas de non récupération à J29, **arrêt du traitement** *	1er épisode : réduction de dose à 150 mg/m² 2ème épisode : maintien de la dose à 150 mg/m² 3ème épisode : **arrêt du traitement**	1er épisode : pas de réduction de dose 2ème épisode : réduire la dose à 60 mg/m² 3ème épisode : **arrêt du traitement**	1er épisode : supprimer le bolus de J1
Plaq < 75x10^9 /l	Retarder le traitement jusqu'à récupération (plaq ≥75x10^9 /l). En cas de non récupération à J29, **arrêt du traitement**	1er épisode : pas de réduction de dose 2ème épisode : diminuer la dose à 150 mg/m² 3ème épisode : **arrêt du traitement**	1er épisode : diminuer la dose à 60 mg/m² 2ème épisode : maintien de la dose réduite 3ème épisode : **arrêt du traitement**	1er épisode : diminuer la dose du bolus et de la perfusion continue de 25%

* *si pas de récupération après 2 retards de cure, arrêt du traitement sauf en cas de bénéfice clinique évident : le cas sera alors discuté avec le coordinateur de l'étude et le promoteur.*

TRAITEMENT B : GEMCITABINE

NFS avant chaque administration	RETARD DE CYCLE	RÉDUCTION DE DOSE
Granulocytes > 1 x 10^9 /l **et** plaq > 100 x 10^9 /l	Pas de retard de cycle	Administrer 100 % de la dose totale
0,5 < Granulocytes ≤ 1 x 10^9 /l **ou** 50 < plaq ≤ 100 x 10^9 /l	Pas de retard de cycle	Administrer 75 % de la dose totale (réduction de dose de 25%)
Granulocytes ≤ 0,5 x 10^9 /l **ou** plaq ≤ 50 x10^9 /l	Retarder la cure jusqu'à récupération de 500 granulocytes et 50 000 plaq	Pas de réduction de dose

6.3.1.2 Selon la toxicité hématologique de l'intercure (nadir) dans le bras Folfirinox

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
-Neutropénie fébrile isolée -Neutropénie G4 de plus de 7 jours -Infection avec neutropénie de grade 3-4 concomitante	1er épisode : réduire la dose de CPT-11 à 150 mg/m^2 et supprimer le bolus de 5-FU à J1 2ème épisode : malgré la réduction de dose de CPT-11 et la suppression du bolus de 5-FU, réduire la dose de L-OHP à 60 mg/m^2 3ème épisode : **arrêt du traitement**
Thrombopénie grade 3-4	1er épisode : réduire la dose L-OHP à 60 mg/m^2 et la dose de 5-FU continu de 25 % 2ème épisode : malgré la réduction de dose à 60 mg/m^2, réduire la dose de CPT-11 à 150 mg/m^2 et la dose de 5-FU continu de 25 % supplémentaires 3ème épisode : **arrêt du traitement**

6.3.2 Toxicités digestives dans le bras Folfirinox

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
-Diarrhée grade **3-4** isolée ou -Diarrhée + fièvre et/ou neutropénie grade 3-4	1er épisode : réduire la dose de CPT-11 à 150 mg/m^2 et supprimer le bolus de 5FU à J1 2ème épisode : malgré la diminution de dose du CPT-11 à 150 mg/m^2, réduire la dose de L-OHP à 60 mg/m^2 et réduire la dose de 5FU continu de 25 % 3ème épisode : **arrêt du traitement**
Diarrhée résistante (> 48 h) en dépit des hautes doses de lopéramide	Pas de réduction de dose du CPT-11 ni de L-OHP ni de 5-FU après récupération sauf si diarrhée grade 3-4, ou diarrhée + fièvre et/ou neutropénie grade 3-4

6.3.3 Mucites ou syndrome « main-pied » dans le bras Folfirinox

Ces toxicités sont le fait du 5-FU.
En cas de toxicité grade 3-4, une réduction de posologie de 25 % du 5-FU bolus et du 5-FU continu sera réalisée pour les cures suivantes.

6.3.4 Toxicité cardiaque

En cas d'angine de poitrine ou d'infarctus du myocarde, le traitement sera arrêté.

6.3.5 Neuropathie périphérique

Pour jugés la toxicité évaluables, les patients doivent avoir reçu au moins une cure ou une prise de traitement. L'échelle spécifique modifiée de Lévi et al. (37) n'étant pas assez précise, la toxicité neurologique sera évaluée selon l'échelle de toxicité NCI version 3.0 (annexe 5).

La toxicité neurologique de l'oxaliplatine demande une attention particulière et il faut signaler que sa cotation est complexe avec les critères CTC NCI version 3.0. Les différentes toxicités neurologiques peuvent être classées ainsi:

- Acro-dysesthésies au froid, sans douleurs ou dysesthésies (picotements, fourmillements) : sera coté en "Neuropathy, Sensory"
- Troubles moteurs objectifs découverts par l'examen clinique ou symptomatique : sera coté en "Neuropathy, Motor"
- Douleurs des mâchoires, crampes, neuropathies douloureuses : ne pas oublier de coter en plus en "Pain"

Si l'oxaliplatine est arrêté pour neurotoxicité, l'irinotécan et le 5-FU seront poursuivis.

6.3.6 Adaptation de dose pour élévation de la bilirubine

En cas d'élévation de la bilirubine il est nécessaire de prévoir une adaptation de dose de l'irinotécan.

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
35 < Bilirubine ≤ 50 µmol/l	réduire la dose de CPT-11 à 75%
Bilirubine > 50 µmol/l	réduire la dose de CPT-11 à 50%

6.3.7 Autres toxicités

Toute autre toxicité ≥ grade 2, exceptées l'anémie et l'alopécie, pourra justifier une réduction de dose de chacun des protocoles si indiqué médicalement :

- Traitement A Folfirinox : réduction du CPT11 à 150 mg/m^2 et/ou L-OHP à 60 mg/m^2 et/ou le 5-FU de 25 % en fonction du type de toxicité
- Traitement B gemcitabine : réduction de dose de 25%

6.4 Traitements symptomatiques des toxicités

6.4.1 Le syndrome cholinergique

En cas de syndrome cholinergique aigu (hypersudation, hypersalivation, troubles visuels, larmoiements, myosis, crampes abdominales, diarrhée précoce) une injection par voie sous cutanée de 0,25mg d'atropine sera réalisée à titre curatif puis ensuite à titre préventif aux cures suivantes, sauf contre indication pour les patients traités par CPT-11.

6.4.2 La diarrhée tardive

Traitement prophylactique :

Aucun traitement prophylactique ne doit être donné, en particulier le lopéramide ne doit pas être administré de façon prophylactique. Cependant les patients doivent arrêter tout traitement laxatif et éviter les aliments et les boissons qui sont connus pour accélérer le transit intestinal.

Traitement curatif :

- dès la 1ère selle liquide ou molle le patient doit prendre immédiatement 2 capsules de lopéramide per os puis 1 capsule toutes les 2 h pendant au moins 12 h après la dernière selle liquide, sans dépasser un traitement total d'une durée de 48 h. La prise de boissons riches en électrolytes sera indiquée aussi au patient pendant tout l'épisode de diarrhée.

- En cas de persistance de la diarrhée plus de 48 h en dépit du traitement recommandé par lopéramide, une antibiothérapie à large spectre (fluoroquinolone) sera entreprise pour une durée systématique de 7 jours et après avis médical.

- En cas de diarrhée persistante et/ou sévère, le patient sera hospitalisé pour réhydratation parentérale et le lopéramide sera remplacé par un autre traitement antidiarrhéique laissé au choix du médecin investigateur.

- L'antibiothérapie orale par fluoroquinolone doit aussi être prescrite en cas de diarrhée grade 4 ou de diarrhée associée à une neutropénie de grade 3-4 ou à une fièvre.

- Les patients qui présentent des vomissements ou une fièvre ou un performance status > 2 concomitant à la diarrhée seront hospitalisés rapidement pour support parentéral. Le lopéramide et la fluoroquinolone doivent être prescrits au patient dès sa sortie d'hôpital afin qu'il ait l'un et l'autre à sa disposition dès l'apparition d'une diarrhée.

6.4.3 La neutropénie

En cas de neutropénie sévère c'est-à-dire grade 3-4, les patients sont à haut risque de neutropénie fébrile et d'infection notamment en cas de diarrhée concomitante. En cas d'apparition de ces symptômes, des adaptations posologiques sont prévues au cycle suivant (cf § 6.3.2).

L'administration de facteurs de croissance hématopoïétiques n'est pas recommandée au 1er cycle mais cependant ils peuvent être indiqués au cas par cas selon l'état clinique du patient. Un traitement par filgrastim (Neupogen®) est alors conseillé selon les recommandations jointes en annexe 10.

En cas d'anémie (par ex. taux d'hémoglobine ≤ 11 g/dl), un traitement par darbepoetin alfa (Aranesp®) sera mis en route selon les recommandations jointes en annexe 11.
Il est recommandé de ne pas administrer l'Aranesp® si le taux d'hémoglobine est > à 11 g/dL. Il est nécessaire de veiller à ce que ce taux ne dépasse pas 13 g/dL. En cas d'augmentation de taux d'hémoglobine de plus de 2 g/dL en quatre semaines, réduire la posologie de 25 à 50 %.

6.4.4 L'extravasation

Des réactions sévères liées à une extravasation de l'irinotecan ou d'oxaliplatine ont été rapportées (36). Les recommandations d'ordre général en cas d'extravasation sont les suivantes :
- arrêter immédiatement la perfusion,
- ne pas retirer l'aiguille ou le cathéter,
- aspirer par la même aiguille le maximum de produit infiltré,
- appliquer de la glace sur la zone infiltrée pendant 15 à 20 minutes toutes les 4 à 6 heures pendant 72 h,
- corticothérapie locale,
- vérifier régulièrement le site infiltré pendant les jours suivants, afin de vérifier si quelque traitement est nécessaire. Ne pas hésiter à prendre un avis chirurgical en cas de doute.

6.4.5 Nausées et vomissements

Avant l'administration de l'oxaliplatine une association de corticoïdes (30mn avant) et d'anti 5HT3 (sétron, 15mn avant) est recommandée.

Une prévention des nausées et vomissements retardés est également recommandée, utilisant du métoclopramide (ou un sétron) et éventuellement des corticoïdes.
ATTENTION : En cas de diabète, l'utilisation des corticoïdes doit être faite avec la plus grande prudence.

6.4.6 L'alopécie

Les casques réfrigérants du cuir chevelu sont autorisés, sauf en cas de métastases osseuses de la voûte du crane.

6.5 Traitements concomitants

Aucun traitement à visée antitumorale (chimiothérapie, hormonothérapie, modificateurs de la réponse biologique) ne sera utilisé.
Tous les traitements symptomatiques nécessaires au confort du patient (antiémétiques, antidiarrhéiques) sont autorisés et leur nature, leur posologie et leur durée d'administration, de même que tout autre traitement justifié par une indication médicale.
Les corticoïdes sont proscrits sauf en cas d'indication en urgence ou à visée antiémétique. Leur utilisation sera faite dans la plus grande prudence pour les patients diabétiques.
Une radiothérapie à visée antalgique est aussi autorisée (moelle osseuse irradiée < 20 %). Si la seule cible mesurable devait être irradiée, le patient arrêterait le traitement.

L'association de la warfarine (Coumadine®) avec un protocole FOLFOX est déconseillée (50). Il vaut mieux avoir recours à l'héparine et à ses dérivés. Si la warfarine ne peut être évitée, il faut contrôler plus fréquemment le taux de prothrombine et surveiller l'INR.

Le métronidazole et l'ornidazole augmentent la toxicité du 5-fluorouracile par diminution de sa clairance.

Risque de survenue de convulsion par interaction entre la phénytoïne et l'oxaliplatine. La phénytoïne est donc contre indiquée.

7 . BILAN D'INCLUSION ET DE SUIVI DES PATIENTS

La surveillance des patients depuis la date de tirage au sort et le calendrier des évaluations des patients sont décrits en annexe 2.

7.1 Bilan d'inclusion

Les patients éligibles pour l'essai et ayant signé leur consentement de participation devront subir un bilan initial **dans les 8 jours** précédant le début du traitement, hormis les examens du bilan paraclinique qui pourront être réalisés **dans les 3 semaines** précédant la randomisation.

- **Examen clinique**
  Examen clinique avec détermination du poids, de la taille et de la surface corporelle,
  Indice de performance ECOG (annexe 3),
  Recueil des traitements concomitants.

- **Examen paraclinique**
  Scanner thoraco-abdominopelvien,
  ECG

- **Examens biologiques**
  Hématologie et Coagulation : NFS, plaquettes, TP, TCK,
  Ionogramme sanguin, calcémie
  Bilan hépatique (bilirubine totale, libre et conjuguée, ALAT, ASAT, Phosphatases alcalines, LDH),
  Créatininémie, urée
  Glycémie
  Protidémie, albuminémie, glycosurie
  CA 19-9, ACE
  Test de grossesse si femme en âge de procréer et n'utilisant pas de procédé contraceptif

- **Questionnaire qualité de vie**
  Un questionnaire QLQ - C30 devra être rempli par le patient le jour de la signature du consentement à l'hôpital. Il peut donc être renseigné le jour même ou **dans les 15 jours** précédant la randomisation.

7.2 Bilans de suivi

Les patients seront revus toutes les semaines ou toutes les 2 semaines selon le bras de traitement

7.2.1 Bras A- FOLFIRINOX

A J 8 du premier cycle
- NFS plaquettes, Créatininémie, Kaliémie

Avant chaque cycle : tous les 14 jours
Les patients traités par FOLFIRINOX seront revus avant chaque reprise de cycle pour un bilan clinique afin d'évaluer les toxicités et de déterminer la reprise du traitement.
- évaluation de la tolérance pendant l'intercure
- vérification de la récupération d'éventuelles toxicités au niveau initial ou grade ≤ 1 (sauf alopécie)
- examen clinique complet, avec poids et OMS
- NFS, plaquettes
- Questionnaire de qualité de vie
- Protidémie, ionogramme, créatininémie, urée, glycémie
- Bilirubine totale, libre et conjuguée (au moins tous les mois)
- Questionnaire de qualité de vie EORTC QLQ-C30

Cependant en fonction de la tolérance, des visites de consultation supplémentaires seront possibles.

Tous les examens révélant une toxicité liée au traitement doivent être répétés périodiquement jusqu'à réversion de la toxicité ou jusqu'à ce quelle soit présumée irréversible

7.2.2 Bras B- gemcitabine

Avant chaque administration : tous les 7 jours jusqu'à J43
Les patients traités par gemcitabine seront revus avant chaque administration pour un bilan clinique afin d'évaluer les toxicités et décider de la poursuite du traitement.
- évaluation de la tolérance
- vérification de la récupération d'éventuelles toxicités au niveau initial ou grade ≤ 1 (sauf alopécie)
- NFS, plaquettes

Tous les 15 jours
- vérification de la récupération d'éventuelles toxicités au niveau initial ou grade ≤ 1 (sauf alopécie)
- examen clinique complet, avec poids et OMS
- NFS, plaquettes,
- Bilirubine totale, libre et conjuguée, phosphatases alcalines, ASAT, ALAT
- Urée, Créatininémie
- Ionogramme sanguin, Calcémie, protéines totales
- Questionnaire de qualité de vie EORTC QLQ-C30

7.3 Bilans à 8 semaines de traitement (autour de J 50) pour les 2 bras puis toutes les deux mois

- examen clinique complet, avec appréciation du poids , de l'état général OMS et des différentes toxicités
- **Bilan biologique avec :**
  NFS, plaquettes,

Bilan hépatique complet (bilirubine totale, libre et conjuguée, phosphatases alcalines, ASAT, ALAT)
Ionogramme sanguin, glycémie
Créatininémie, urée
Protidémie

- **Marqueurs tumoraux :**
  ACE, CA 19-9 (uniquement le marqueur le plus significatif lors du bilan initial : choisir le marqueur qui a la valeur initiale la plus importante par rapport à la normale)

- **Evaluation comparative des lésions tumorales :**
  Scanner thoracoabdomino-pelvien (selon les cibles initiales)

- Questionnaire de qualité de vie EORTC QLQ-C30

7.4 Bilans de suivi après reprise du traitement (à partir de J57)

Les patients seront suivis après reprise du traitement selon les mêmes modalités que décrites dans le § 7.2, avec remise d'un questionnaire de qualité de vie tous les 15 jours, un examen scanographique, un bilan hépatique, une créatininémie, et un dosage de ACE ou Ca 19-9 tous les 2 mois.

7.5 Bilans de suivi après les 6 mois de traitement

Les patients sans progression ayant eu les 6 mois de traitements seront suivis tous les 2 mois. Seront évalués la qualité de vie avec remise du questionnaire EORTC QLQ-C30 et la durée de réponse ou de stabilisation, grâce à une imagerie.

7.6 suivi à long terme

Les patients ayant progressé seront suivis tous les 6 mois jusqu'au décès. Seront évalués : les effets toxiques à long terme et la survie. Si un autre traitement est établi, il devra être rapporté.

8 ARRET PREMATURE DU TRAITEMENT

Les patients peuvent arrêter prématurément le traitement pour les raisons suivantes :

- toxicité,
- progression de la maladie,
- retrait de consentement,
- perdu de vue,
- violation majeure de protocole.

Dans la mesure du possible, les patients ayant arrêté prématurément leur traitement seront suivis selon les mêmes modalités que les autres patients.

9 . CRITERE D'EVALUATION

9.1 Critère principal de la phase II

Sera prise en compte la meilleure réponse enregistrée entre le début du traitement et la progression de la maladie ou la dernière évaluation (meilleure réponse globale optimale).
La réponse est définie selon les critères RECIST (annexe 4).

Toutes les réponses objectives doivent être confirmées 4 semaines après leur observation par un nouvel examen.

9.2 Critères secondaires de la phase II

9.2.1 Toxicité

Pour être jugés évaluables pour la toxicité, les patients doivent avoir reçu au moins perfusion de chimiothérapie

- La toxicité est évaluée selon l'échelle de toxicité NCI version 3.0 (annexe 5)

9.3 Critère principal de la phase III

9.3.1 Efficacité

Le critère principal de cette phase sera la durée de survie globale.

9.4 Critères secondaires de la phase III

9.4.1 Survie sans progression

La survie sans progression est calculée de la date de randomisation à la date de première mise en évidence d'une progression documentée, la date du décès, ou la date des dernières nouvelles.

9.4.2 Taux de réponse

Sera prise en compte la meilleure réponse enregistrée entre le début du traitement et la progression de la maladie ou la dernière évaluation (meilleure réponse globale optimale).
La réponse est définie selon les critères RECIST (annexe 4).

Toutes les réponses objectives doivent être confirmées 4 semaines après leur observation par un nouvel examen.

Un comité indépendant de 2 radiologues experts relira toutes les évaluations tumorales radiologiques pour confirmer les réponses enregistrées.

9.4.3 Toxicité

Pour être jugés évaluables pour la toxicité, les patients doivent avoir reçu au moins une cure ou une injection de traitement.

- La toxicité est évaluée selon l'échelle de toxicité NCI version 3.0 (annexe 5).

9.4.4 Qualité de vie

La qualité de vie sera mesurée grâce au questionnaire EORTC QLQ-C30 (39) (annexe 9), et analysée conformément aux spécifications du Groupe Qualité de Vie de l'EORTC (43)

L'analyse principale portera sur les domaines de qualité de vie qui sont habituellement les plus altérés. Les échelles les plus détériorées sont « santé globale / Qualité de vie » (questions 29 et 30), fatigue, douleur, forme physique, état psychologique, activités quotidiennes (38). Les changements sous traitement de la « santé globale/ Qualité de vie » seront considérés comme l'objectif principal et les autres critères comme des objectifs secondaires. Les autres domaines du QLQ-C30 seront analysés uniquement à visée exploratoire. (43)

Le questionnaire EORTC-PAN 24, spécifique de cancer du pancréas ne sera pas utilisé car ce questionnaire n'est pas encore validé et il n'a pas fait l'objet d'une adaptation transculturelle, ce qui le rend inadapté à des patients de langue française.

10 EVENEMENTS INDESIRABLES GRAVES

10.1 Définition Générale

N'est pas considéré comme un événement indésirable grave (EIG) :

- Une hospitalisation < à 24 heures,
- Une hospitalisation programmée préalablement au début de l'essai et/ou prévue par le protocole (biopsie, chimiothérapie..).

Est considéré comme un événement indésirable grave (EIG) tout évènement :

- Entraînant le décès,
- Mettant en jeu le pronostic vital,
- Entraînant une hospitalisation ou une prolongation d'hospitalisation,
- Provoquant une invalidité permanente ou une incapacité temporaire grave,
- Provoquant une anomalie congénitale, une malformation fœtale ou un avortement,
- Médicalement significatif.

  Les termes *invalidité et incapacité* correspondent à tout handicap physique ou psychique temporaire ou permanent, cliniquement significatif et retentissant sur l'activité physique et/ou la qualité de vie du patient.

  Est considéré comme *médicalement significatif* tout événement clinique ou résultat de laboratoire considéré comme grave par l'investigateur et ne correspondant pas aux critères de gravité définis ci-dessus. Ils peuvent faire courir un risque au patient et nécessitent une intervention médicale pour prévenir une issue correspondant à l'un des critères de gravité mentionné précédemment *(exemples : surdosages, seconds cancers, grossesses et faits nouveaux peuvent être considérés comme médicalement significatifs*).

10.2 Définition d'un événement indésirable grave attendu (EIG-A)

Un EIG-A est un événement déjà mentionné dans la version la plus récente de la brochure investigateur ou dans le résumé des caractéristiques du produit (RCP) pour les médicaments *ayant déjà une autorisation de mise sur le marché (AMM).* Cette définition s'applique également au médicament de l'essai lorsqu'il est administré *pour une même population hors indication de l'AMM.*

10.3 Définition d'un événement indésirable grave inattendu (EIG-I)

Un EIG-I est un événement non mentionné ou différent par sa nature, son intensité, son évolution par rapport à la brochure investigateur ou au résumé des caractéristiques du produit (RCP) pour les médicaments ayant une autorisation de mise sur le marché (AMM).

10.4 Critère d'intensité

Le critère d'intensité ne doit pas être confondu avec le critère de gravité qui sert de guide pour définir les obligations de déclaration.

L'intensité des événements sera estimée selon la classification NCI-CTC version 3.0 (toxicité de grade 1 à 5). L'intensité des évènements indésirables non listés dans cette classification sera appréciée selon les qualificatifs suivants :

Légère (grade 1) : n'affecte pas l'activité quotidienne habituelle du patient
Modérée (grade 2) : perturbe l'activité quotidienne habituelle du patient
Sévère (grade 3) : empêche l'activité quotidienne habituelle du patient
Très Sévère (grade 4) : impose des mesures de réanimation/ menace le pronostic vital
Décès (grade 5)

10.5 Conduite à tenir en cas d'événement indésirable grave

L'investigateur informe la pharmacovigilance du BECT (PV-BECT) de tous les **Evènements Indésirables Graves Attendus (EIG-A) et inattendus (EIG-I),** qu'ils soient imputables ou non à la recherche, qui se produisent durant l'étude ou dans les 30 jours suivant la dernière administration du traitement.

Tous les Événements Indésirables Graves retardés (survenant après cette période de 30 jours) considérés comme raisonnablement liés au(x) traitement(s) protocolaire ou à la recherche doivent être déclarés sans limitation de délai.

La déclaration se fait par envoi par fax à la PV du BECT du formulaire de "***notification d'un événement indésirable grave"*** (cf annexe n° 6) documenté le plus précisément poss ible, daté et signé, dans les **48 heures** ouvrées suivant leur constatation au :

Bureau d'Etudes Cliniques et Thérapeutiques
Pharmacovigilance
Tél. : 01 44 23 04 16 – Fax : 01 44 23 55 70
Courriel : pv-bect@fnclcc.fr

L'investigateur notera pour chaque évènement :

- Sa description aussi clairement que possible selon la terminologie médicale,
- Si l'évènement est attendu ou inattendu,
- L'intensité,
- La date de début et de fin de l'événement,
- Les mesures entreprises et la nécessité ou non d'un traitement correcteur,
- Si le traitement de l'essai a été interrompu,

- Son évolution. En cas d'évènement non fatal, l'évolution devra être suivie jusqu'à la guérison ou le retour à l'état antérieur ou à la stabilisation d'éventuelles séquelles,
- La relation de causalité entre cet évènement et le traitement à l'essai ou une contrainte liée à la recherche (période sans traitement, examens complémentaires demandés dans le cadre de la recherche etc ..),
- La relation de causalité avec le(s) médicaments de l'essai, la pathologie traitée, une autre pathologie ou un autre traitement.

L'investigateur doit également joindre au rapport d'évènement indésirable grave, à chaque fois que possible :

- Une copie du compte-rendu d'hospitalisation ou de prolongation d'hospitalisation,
- Une copie du rapport d'autopsie ,
- Une copie de tous les résultats d'examens complémentaires réalisés, y compris les résultats négatifs pertinents en y joignant les valeurs normales du laboratoire,
- Tout autre document qu'il juge utile et pertinent.

Tous ces documents doivent être anonymisés.

Des compléments d'informations pourront être demandés (par fax, par téléphone ou lors d'une visite) par le moniteur.

En cas d'**EIG inattendu et raisonnablement relié à un des traitements de l'étude, un complément d'information sera demandé par la pharmacovigilance à l'investigateur.** Celui-ci devra adresser au promoteur dans les **48 heures** le formulaire ***"complément d'information d'un EIG inattendu"*** (cf annexe n°6 bis) dûment renseigné.

Une liste des EIG attendus, établie à partir des RCP des produits est annexée à ce protocole (cf annexe 12).

D'autre part, une liste synthétique des EIG attendus, établie à partir du RCP et reclassée selon l'échelle de toxicité NCI-CTC V3, sera jointe au cahier d'observation afin de faciliter le remplissage du formulaire EIG par l'investigateur.

Néanmoins, tout événement attendu mais différent par son intensité, son évolution ou sa fréquence sera considéré comme inattendu par la pharmacovigilance.

10.6 Suivi des EIG

L'investigateur est responsable du suivi médical approprié des patients jusqu'à la résolution ou la stabilisation de l'effet ou jusqu'au décès du patient. **Cela peut impliquer parfois que ce suivi se prolonge après la sortie du patient de l'essai.**

Il transmet les informations complémentaires à la PV du BECT à l'aide d'un formulaire de déclaration des EIG (en cochant la case Suivi n° X pour préciser qu'il s'agit d'un follow-up et non d'un rapport initial) dans les 48 heures suivant leur obtention. Il transmet également le dernier suivi à la résolution ou à la stabilisation de l'EIG.

Il conserve les documents concernant l'effet indésirable présumé afin de permettre, en cas de nécessité de compléter les informations précédemment transmises.

Il répond aux demandes d'informations complémentaires de la PV du BECT afin de documenter l'observation initiale.

11 . DETERMINATION DU NOMBRE DE PATIENTS ET ANALYSE STATISTIQUE

11.1 Nombre de sujets nécessaires en phase II

On décide de conclure à l'efficacité du Folfirinox si le taux de réponses objectives est supérieur ou égal à 24 % et de conclure à son inefficacité si ce taux est inférieur ou égal à 10 %. Le calcul du nombre de sujets est effectué en utilisant la procédure de Fleming multi-étapes (27). On décide d'inclure au plus 44 sujets en 3 étapes par bras, soit 88 patients en tout (puissance de 92% formulation bilatérale, au seuil 5 %).

Dans le bras expérimental (Folfirinox):

- A la fin de la 1ère étape (20 malades inclus) :
  - si l'on a observé 2 réponses objectives (RO) ou moins, on arrêtera l'essai en concluant que le Folfirinox n'est pas efficace.
  - si l'on a observé 8 réponses objectives ou plus, passera à la phase III.
  - si l'on a observé entre 3 et 7 réponses objectives, on continuera la phase II : inclusion de 10 malades supplémentaires.

- A la fin de la 2ème étape (30 malades en tout) :
  - si l'on a observé 4 réponses objectives ou moins, on conclura que le Folfirinox n'est pas efficace.
  - si l'on a observé 11 réponses objectives ou plus, on conclura que le Folfirinox est efficace et on passera en phase III.
  - si l'on a observé entre 5 et 10 réponses objectives, on continuera l'essai : inclusion de 10 malades supplémentaires.

- A la fin de la 3ème étape (40 malades en tout) :
  - si l'on a observé 6 réponses objectives ou moins, on conclura que le Folfirinox n'est pas suffisamment efficace et on ne passe pas en phase III.
  - s'il y a 12 réponses, on poursuivra l'étude en phase III.
  - si après 40 malades il n'y a pas de conclusion, on passera alors en phase III en incluant le nombre de patients supplémentaires.

Ce plan a une puissance égale à 0.92 (on a 92 chances sur 100 de conclure à l'efficacité si le taux de réponses objectives est égal à 60%). Le risque alpha est égal à 0.05 (on a 5 chances sur 100 de conclure à l'efficacité si le taux de non progression est égal à 35%).

11.2 Nombre de sujets nécessaires en phase III

Pour mettre en évidence une différence dans les médianes de survie de 3 mois (passage de 7 à 10 mois de médiane), soit un risque relatif de 0.70, il faudra **inclure 360 patients** pour maintenir un risque global alpha de 5 %, en acceptant un risque beta de 20 % (puissance de l'essai = 80%).
Cette puissance sera obtenue lorsque **250 événements** auront été observés (calcul effectué avec le logiciel East 5).

11.3 Analyse statistique

L'analyse statistique finale devra être réalisée lorsque **250 événements** auront été observés

Les données seront présentées sous forme de :

1. pourcentages (variables qualitatives),
2. moyenne et écart type ou médiane et extrêmes (variables quantitatives),

3. courbes de survie estimées par la méthode de Kaplan Meier (données de survie) (27). La date d'origine sera la date du tirage au sort.

Les résultats concernant le critère principal et les critères secondaires seront présentés avec un intervalle de confiance à 95% (Rothman pour les données de survie).

On comparera :

1. les variables qualitatives par un test du χ^2 ou par un test de Fisher,
2. les variables quantitatives par un test t de Student ou par un test non paramétrique (Wilcoxon),
3. les données de survie par un test du log-rank.

Ces comparaisons seront ajustées sur les facteurs de stratification.
Tous les tests seront bilatéraux au seuil 5 %.

Les analyses statistiques seront réalisées avec le logiciel Stata v10.

11.4 Non respect du protocole

On n'acceptera aucune exclusion. Les sujets inclus à tort et les sujets qui ne respecteront pas le protocole seront pris en compte dans l'analyse selon leur groupe de randomisation (analyse en intention de traiter).
Afin de limiter le nombre de perdus de vue, l'investigateur de chaque centre se chargera de reconvoquer les malades ne s'étant pas présentés aux consultations de surveillance.

11.5 Analyses intermédiaires et surveillance de l'essai

Une analyse intermédiaire d'efficacité sera réalisée lorsque 2/3 des événements (décès) auront été observés soit **167 événements**.
Afin de maintenir un risque global de 5%, cette analyse intermédiaire ne sera considérée comme significative que si la p-value est inférieure ou égale à 0,001 et **p≤0,049** à l'analyse finale.

Le Comité de Surveillance (IDMC) pourra proposer l'arrêt prématuré de l'essai s'il le juge nécessaire et si l'ensemble des données disponibles provenant de l'essai ou d'autres sources est suffisamment convaincant pour influencer les pratiques thérapeutiques de la majorité des médecins.

12 . COUT ET SURCOUT DE LA RECHERCHE

Les éventuels frais supplémentaires visés à l'article R.1121-1 du Code de la Santé Publique font l'objet d'une convention négociée entre la FNCLCC et le représentant de l'établissement en tenant compte des moyens financiers dont dispose la FNCLCC dans le cadre de son activité de promotion publique.

Cependant, la FNCLCC assure l'organisation de l'essai et la prise en charge de la fourniture du matériel suivant : protocole, cahier d'observation, dossier investigateur ; ainsi que la fourniture des produits à l'étude irinotécan et oxaliplatine.

Le matériel, les traitements, ou une prestation fournis par d'autres partenaires, doivent être précisés dans la convention de l'essai.

13 . ASSURANCE QUALITE ET COMITE INDEPENDANT

Le promoteur est responsable de la mise en place d'un système d'assurance qualité décrit dans les procédures fédérales, afin que l'essai soit réalisé conformément au protocole et aux BPC.
Une revue centralisée du critère d'efficacité sera réalisée par un comité d'experts indépendants.

14 . REGLES DE PUBLICATIONS PRODIGE

La publication des essais PRODIGE dans un délai rapide par une revue de qualité est un objectif essentiel pour le progrès de la thérapeutique. Cette publication se fait sous la responsabilité du Comité de Coordination du PRODIGE (CCP), qui décide :

- du moment de la publication des résultats préliminaires et des résultats définitifs d'une étude. .
- de la composition d'un Comité de Rédaction (5 membres au maximum).

Toutes les informations résultant d'essais sont considérées comme confidentielles, au moins jusqu'à ce que l'analyse appropriée et le contrôle par le promoteur, l'investigateur coordonnateur et le statisticien de l'essai soient achevés.

Le Comité de Coordination (CCP) peut déléguer ces fonctions au coordonnateur de l'essai.

En tout état de cause, le CCP valide les choix faits et veille à ce que les délais soient tenus. L'absence de réponse du CCP dans un délai d'un mois après soumission du Comité de Rédaction vaut acceptation.

1) Le Comité de Rédaction comprend :

- Le coordinateur (ou les coordinateurs s'ils sont deux) qui a écrit le premier projet. Il sera sauf exception le rédacteur principal
- Le(s) statisticien(s) ayant effectué l'analyse des données
- Les contributeurs les plus importants
- Eventuellement un spécialiste ayant fourni une contribution essentielle à l'analyse des données (biologiste, anatomopathologiste,...)

2) Le rédacteur principal s'engage à soumettre pour publication dans un délai déterminé par le CCP. Ce délai ne devrait pas dépasser une année après la clôture d'un essai. S'il n'est pas en mesure de le faire, le CCP désigne un nouveau rédacteur qui deviendra le premier auteur. Pour aider à l'écriture des articles issus des essais, il pourra être fait appel à un rédacteur médical et organisé des ateliers d'écriture pour le rédacteur principal, en collaboration avec le statisticien.
Avant toute publication la liste des inclusions par centre et la liste des investigateurs de chaque centre pour l'essai considéré sera mise à la disposition des investigateurs de l'essai.

3) Les auteurs de la publication sont dans l'ordre en fonction du travail fourni et du nombre de patients inclus :

- Le rédacteur principal
- Les membres du Comité de Rédaction de l'article (voir ci-dessus)
- Un nombre limité d'investigateurs (1 par centre) dans l'ordre de leur participation, et en règle 1 seul par centre mais pour certains centres le Comité Directeur peut décider 2 investigateurs. Cette règle pourra être pondérée pour permettre à certains centres petits et moyens ayant fait un gros effort d'inclusion de figurer parmi les auteurs. Le CCP validera cette pondération afin que personne ne soit lésé.
- Le nombre maximum d'auteurs autorisés par les revues sera utilisé.
- Quel que soit le nombre de malades inclus, il y aura au moins un auteur représentant un des deux partenaires (FFCD ou FNCLCC)
- Dans le cas d'une publication dérivée ou d'un travail annexe, les auteurs pourront être différents de ceux de l'article princeps et refléter la spécialité intéressée par l'article Ex :

dans les essais de RCT un article dédié à la radiothérapie peut être signé par des radiothérapeutes co-investigateurs des centres ayant inclus. Le dernier auteur de cette publication dérivée (éventuellement en « equally contributed ») est le premier signataire de l'article princeps.

- Le partenariat Prodige est cité dans le titre ou après les auteurs. En cas d'essai coopératif, la première association citée est celle qui a initié l'essai et les autres sont mentionnées à condition qu'elles aient inclus au moins 5 % des patients, dans l'ordre de leur participation.
- Sauf exception, pour les essais promus ou gérés par la FFCD un membre de l'unité Inserm U 866 sera dernier auteur, s'il n'est pas rédacteur principal, afin d'assurer la prise en compte de ce travail par l'Inserm. Dans ce cas l'avant-dernier auteur pourra être signalé comme ayant « equally contributed », si c'est applicable à la revue concernée.
- Le statisticien sera dans les auteurs, en règle générale au delà de la 3^{e} place. Il pourra être le 1er ou 2^{e} auteur d'une publication spécifique.

Tous les participants ne figurant pas dans les auteurs sont cités en fin d'article. Le gestionnaire de l'étude (Data manager) est également cité. Il peut être dans les auteurs si le CCP l'estime justifié.
Les partenaires sont remerciés.
Les auteurs et le promoteur reçoivent un manuscrit pour critique avant l'envoi à une revue. Ils s'engagent à répondre dans les 15 jours ouvrables pour que leur avis soit pris en compte (30 jours en période estivale).

4) Communication orale à partir des résultats de l'essai :

Un investigateur peut, avec l'accord du CCP et du Comité Directeur, présenter en son nom tout ou partie des résultats en communication orale. Les auteurs sont en règle générale les mêmes que pour l'article écrit, mais l'ordre des auteurs pour les articles et les communications peut varier, et varier aussi selon les congrès où la communication est faite. Dans certains cas (études multidisciplinaires, ou études pathologiques, biologiques, écho-endoscopiques parallèles à un essai thérapeutique par exemple) d'autres auteurs pourront être choisi en fonction de leur travail. Le partenariat PRODIGE et les autres associations, le cas échéant, doivent être cités.

15 . ASPECTS ETHIQUES ET REGLEMENTAIRES

L'essai clinique doit être conduit conformément aux principes éthiques de la déclaration d'Helsinki de 1964 révisée à Edimbourg en 2000, aux Bonnes Pratiques Cliniques de la Conférence Internationale d'Harmonisation (ICH–E6, 17/07/96), à la Directive Européenne (2001/20/CE) sur la conduite des essais cliniques, la loi Huriet modifiée (20/12/98) relative à la Protection des Personnes se prêtant à la Recherche Biomédicale ainsi qu'aux dispositions prévues par la Commission Nationale Informatique et Libertés (loi n°94-548 du 1/07/94 complétant la loi n°78-17 du 6/01/78).

15.1 Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale (CCPPRB)

Le protocole d'essai clinique ainsi que les différents amendements ou toute information ou document jugé nécessaire par le promoteur sont soumis par l'investigateur coordonnateur de l'essai à l'avis d'un CCPPRB de la région où il exerce son activité (art. L. 1123-6). Les différents originaux des réponses écrites du CCPPRB doivent être transmis par le coordonnateur au promoteur.

15.2 Information et Consentement des participants

Préalablement à la réalisation d'une recherche biomédicale sur une personne, le consentement libre, éclairé et exprès de celle-ci doit être recueilli après qu'elle ait été informée, par l'investigateur ou son représentant, de l'objectif de la recherche, du déroulement et de la durée de l'étude, des bénéfices, risques potentiels et contraintes de l'essai ainsi que de la nature du produit étudié et de l'avis donné par le CCPPRB (art. L. 1122-1).

Le formulaire de consentement sera daté et signé personnellement par le patient et l'investigateur ou le médecin qui le représente (original archivé par l'investigateur, une copie sera remise au patient ou à son représentant légal).

Le formulaire d'information et de consentement éclairé (annexe 7) destiné au patient doit être associé sur un même document afin d'éviter tout risque de contestation sur le contenu de l'information donnée.

15.3 Responsabilités des investigateurs

L'investigateur principal de chaque établissement concerné s'engage à conduire l'essai clinique conformément au protocole qui a été approuvé par le CCPPRB. L'investigateur ne doit apporter aucune modification au protocole sans l'autorisation du promoteur et sans que le CCPPRB ait donné un avis favorable sur les modifications proposées.

Il est de la responsabilité de l'investigateur principal :

- de fournir au promoteur son curriculum vitae ainsi que ceux des co-investigateurs,
- d'identifier les membres de son équipe qui participent à l'essai et de définir leurs responsabilités,
- de démarrer le recrutement des patients après autorisation du promoteur,
- de faire le maximum pour inclure le nombre requis de patients dans les limites de la période de recrutement établie.

Il est de la responsabilité de chaque investigateur :

- de recueillir le consentement éclairé daté et signé personnellement par le patient avant toute procédure de sélection spécifique à l'essai,
- de compléter régulièrement les cahiers d'observation (CRF) pour chacun des patients inclus dans l'essai et de laisser à l'Assistant de Recherche Clinique (ARC) un accès direct aux documents-source afin que ce dernier puisse valider les données du CRF,
- de dater, corriger et de signer les corrections des CRF pour chacun des patients inclus dans l'étude,
- d'accepter les visites régulières de l'ARC et éventuellement celles des auditeurs mandatés par le promoteur ou des inspecteurs des autorités de tutelle.

Toute la documentation relative à l'étude (protocole, consentements, cahiers d'observation, dossier investigateur, etc...), ainsi que les documents originaux (résultats de laboratoire, radiologies, comptes-rendus de consultations, rapports d'examens cliniques pratiqués, etc.) doivent être détenus dans un lieu sûr et considérés comme du matériel confidentiel. L'archivage des données sera sous la responsabilité de l'investigateur et selon la législation en vigueur.

Ce dernier devra conserver les données ainsi qu'une liste d'identification des patientes pendant une durée minimale de 15 ans après la fin de l'étude.

15.4 Responsabilités du promoteur

Conformément à la loi Huriet, il est de la responsabilité du promoteur de :

- souscrire une assurance garantissant sa responsabilité civile en cas de conséquences dommageables de la recherche pour la personne qui s'y prête (art. L.1121-7),
- s'acquitter auprès de la Direction Régionale des Affaires Sanitaires et Sociales (DRASS) compétente du versement du droit fixe pour la consultation d'un comité de protection des personnes (CCPPRB) (Arrêté du 7/5/91 et du 13/12/01),
- transmettre à l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), la déclaration d'intention initiale décrivant les données essentielles de la recherche accompagnée de l'avis du CCPPRB (art. L.1123-8),
- d'informer les Directeurs (art. L.1123-10, R.5124) et les Pharmaciens (art. L.5125-19, R.5124-1) des établissements de santé,
- communiquer aux investigateurs toutes les informations nécessaires pour la conduite de la recherche (art. R.5122),
- d'informer, dès qu'il en a connaissance, l'AFSSAPS de tout Evénement Indésirable Grave susceptible d'être dû à la recherche ainsi que tout arrêt prématuré de l'étude (art. L.1123-8).

Le promoteur doit également effectuer une déclaration des données médicales nominatives et informatisées, auprès du Comité Consultatif et de la Commission Nationale Informatique et Libertés (CNIL), conformément aux conditions d'application de la procédure simplifiée (Loi n°94-548 du 1/07/94 complétant la Loi n°78-17 du 6/01/78).

Le promoteur doit assurer l'archivage des documents essentiels sur la conduite de l'étude dans des conditions assurant leur sécurité, pendant la durée minimale prévue par les BPC, soit 15 ans après la fin de la recherche.

15.5 Comité de Patients

Le Comité de Patients s'engage dans le cadre des essais cliniques en cancérologie promus par la FNCLCC à relire le protocole et à proposer des améliorations portant notamment sur la qualité de la lettre d'information, la mise à disposition d'un plan de traitement et de surveillance, la suggestion de mesures visant à améliorer le confort des patients et selon la charte qui a été définie entre le Comité de Patients de la Ligue Nationale Contre le Cancer (LNCC) et le BECT de la FNCLCC.

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ANNEXES

ANNEXE 1 :
Modalités de préparation et d'administration des produits

1 – IRINOTECAN (CAMPTO®)

L'irinotécan est un dérivé hémisynthétique de la camptothécine. Il s'agit d'un agent antinéoplasique qui agit comme inhibiteur spécifique de l'ADN topo-isomérase I. L'irinotécan est métabolisé par la carboxylestérase dans la plupart des tissus en un métabolite actif, le SN-38 qui s'est révélé plus actif que l'irinotécan sur la topo-isomérase I purifiée et plus cytotoxique sur plusieurs lignées de cellules tumorales murines ou humaines. L'inhibition de l'ADN topo-isomérase I par l'irinotécan ou le SN-38 induit des lésions simple-brin de l'ADN qui bloquent la fourche de réplication de l'ADN et sont responsables de l'activité cytotoxique. Celle-ci est fonction du temps du contact avec les cellules et est spécifique de la phase S.

Présentation
Solution à diluer pour perfusion, concentrée dans des flacons contenant 40 mg et 100 mg dans 2 ml et 5 ml respectivement, fournissant une solution à 20 mg/ml.

Préparation
Pour préparer la solution de Campto®, prélever, à l'aide d'une seringue graduée, dans le flacon la quantité voulue de la solution de Campto® en veillant à respecter les conditions d'asepsie et l'injecter dans une poche ou un flacon de perfusion de 250 ml contenant soit une solution de chlorure de sodium à 0,9 %, soit une solution glucosée à 5 %. Mélanger soigneusement la solution à perfuser par rotation manuelle.

Conservation
Le produit doit être conservé à l'abri de la lumière.
Après reconstitution, la solution de Campto® ne contenant pas de conservateur, elle doit être utilisée immédiatement après dilution. Cependant, si la dilution est réalisée sous stricte condition aseptique, la solution de Campto® pour perfusion peut être utilisée (temps de perfusion compris) dans les 12 heures, conservée à température ambiante, ou dans les 24 heures, conservée au réfrigérateur (+ 2 ° à + 8 °C) après la préparation.

2 – OXALIPLATINE (ELOXATINE®)

L'oxaliplatine est un agent antinéoplasique, appartenant à une nouvelle classe de platine dans laquelle l'atome de platine est complexé avec un 1,2 diaminocyclohexane (DACH) et un groupe oxalate. L'oxaliplatine est un énantiomère unique, le cis-[oxalato (trans 1-1-1,2-DACH) platine]. L'oxaliplatine présente un large spectre d'activité cytotoxique in vitro et antitumoral in vivo dans divers systèmes de modèles tumoraux, y compris des modèles de cancer colorectal de l'homme. L'oxaliplatine s'est aussi montré efficace, in vitro et in vivo, dans différentes lignées résistant au cisplatine. Une action cytotoxique synergique avec le 5-fluorouracile a été mise en évidence in vitro et in vivo. Les études sur le mécanisme d'action, bien que celui-ci ne soit pas totalement élucidé, montrent que les dérivés hydratés résultant de la biotransformation de l'oxaliplatine interagissent avec l'ADN pour former des ponts intra- et inter-brins entraînant une interruption de la synthèse de l'ADN, cause de l'activité cytotoxique et antitumorale.

Présentation
solution concentrée pour perfusion dosée à 50 mg et à 100 mg,

Préparation
Reconstitution dans de l'eau ppi ou une solution de glucose à 5%, d'une solution contenant 5 mg d'oxaliplatine par ml.
Pour obtenir une concentration en oxaliplatine de 5 mg/ml, ajouter 10 ml de solvant à la solution concentrée à 50 mg, et 20 ml de solvant à la solution concentrée à 100 mg.

Conservation
Dans les conditions d'utilisation, la stabilité physicochimique a été démontrée pendant 48 heures à une température comprise entre + 2 °C et + 8 °C, et à + 30 °C. D'un point de vue microbiologique, la solut ion reconstituée doit être diluée immédiatement dans une solution de glucose à 5 %. Si la dilution n'est pas effectuée immédiatement, les durées et conditions de conservation avant utilisation sont sous la responsabilité de l'utilisateur ; la durée de conservation ne doit normalement pas excéder 24 heures à une température comprise entre + 2 °C et + 8 °C, sauf si la reconst itution a été réalisée dans des conditions aseptiques contrôlées et validées.

3 – 5-FLUOROURACILE

Le Fluorouracile est un antinéoplasique cytostatique de la classe des antimétabolites (antipyrimidine). Afin de mieux comprendre l'activité du fluorouracile, il faut rappeler que l'uracile joue un double rôle fondamental dans les tissus à croissance rapide : d'une part, en étant le précurseur (via la thymidilate synthétase) de la thymine, base nécessaire à la synthèse d'ADN qui préside à la division cellulaire ; d'autre part, en entrant dans la composition des ARNs qui président à la synthèse des protéines et des enzymes cellulaires.

Présentation
Solution à diluer pour perfusion concentrée dans des flacons contenant 250 mg, 500 mg, 1g et 5 g, dans 5 ml, 10ml, 20 ml et 100 ml respectivement, fournissant une solution à 50 mg/ml.

Mode d'administration
Voie intraveineuse. Ne pas administrer par voie intramusculaire. En cas d'extravasation, l'administration sera interrompue immédiatement.
Dilutions : 15 ml de solution injectable peuvent être mélangées à 250 ml des solutions suivantes :
- chlorure de sodium à 0,9%
- glucose à 5%
- glucose à 10%
- glucose à 2,5% + chlorure de sodium à 0,45%
- solution de Ringer
- solution de Hartmann

Conservation
A conserver à une température comprise entre + 15°C et +25°C. Ce médicament est sensible à la lumière. Conserver le conditionnement primaire dans l'emballage extérieur.
Après dilution, une utilisation immédiate est recommandée. Toutefois, la stabilité a été démontrée pendant 8 heures à une température comprise entre + 15°C et + 25°C.

4 - ACIDE L-FOLINIQUE

Antianémique (B : sang et organes hématopoïétiques). L'acide folinique sous sa forme lévogyre représente la forme active du DL-acide folinique. Une dose d'isomère L correspond à la moitié de la dose du composé racémique DL. L'efficacité et les effets indésirables de l'isomère L sont identiques à ceux du composé racémique.
L'acide folinique est un facteur antianémique dérivé de l'acide folique, dont il représente le métabolite actif. C'est un antagoniste biochimique des agents antifoliques tels que le méthotrexate (dont il est l'inhibiteur spécifique), mais aussi de la pyriméthamine et, dans une moindre mesure, la salazopyrine.

Présentation
Le produit est fourni sous forme de lyophilisat pour usage parentéral dosé à 25 mg, et sous forme de solution injectable par voie IM ou IV dosée à 25 mg/2,5 ml.

Conservation
Le lyophilisat est à conserver à une température inférieure à 30 °C, à l'abri de la lumière et de l'hu midité. Après reconstitution : la solution peut être conservée 24 heures à une température inférieure à 30 °C. La solution se conserve au réfrigérateur à une température comprise entre 2°C et 8°C et à l'abri de la lumière.

5 – GEMCITABINE (GEMZAR®)

Présentation
La gemcitabine est fournie sous forme de poudre lyophilisée conditionnée dans des flacons stériles contenant 200 mg ou 1 g d'hydrochlorure de gemcitabine (exprimée sous forme de base libre), du mannitol et de l'acétate de sodium.

Préparation
Le diluant recommandé pour la reconstitution du Gemzar® est une solution de chlorure de sodium à 0,9%.
Les flacons seront reconstitués grâce à l'ajout de sérum salé isotonique pour aboutir à une solution contenant idéalement 10 mg/ml au maximum. La concentration pour les flacons de 200mg et de 1g ne doit pas dépasser 40 mg/ml.

Administration
Une quantité appropriée du produit sera préparée avec du sérum salé isotonique et administrée en perfusion continue pendant 30 minutes.

Conservation
Le produit lyophilisé doit être stocké à moins de 3°C. Une fois le produit reconstitué, il doit être s tocké à température ambiante et utilisé dans les 24 heures. Ne pas stocker le produit reconstitué dans le réfrigérateur.

ANNEXE 2 :
Tableau récapitulatif des investigations

Plan de traitement													
Date	**J1**	**J8**	**J15**	**J22**	**J29**	**J36**	**J43**	**J50**	**J57**	**J64**	**J71**	**J78**	**Jn**
	C1		**C2**		**C3**		**C4**		**C5**		**C6**		**Cn**
Bras A : FOLFIRINOX	*oxaliplatine 85 mg/m² J1+ irinotecan 180 mg/m² J1+ acide folinique 400 mg/m² J1, 5-FU bolus 400 mg/m² J1, 5-FU continu 2,4 g/m² sur 46 heures J1/ J2 de chaque cycle*								*Reprise du traitement selon le schéma précédent, toutes les 2 semaines*				
Bras B : gemcitabine	↑	↑	↑	↑	↑	↑	↑		↑	↑	↑		↑
	gemcitabine 1000 mg/m² de chaque semaine pendant 7 semaines								*Reprise de la gemcitabine 3 semaines sur 4*				

12 cycles prévus pour le bras A = 6 mois de traitement

Plan de surveillance BRAS A Folfirinox									
Visite	**Bilan inclusion**	**Bilans de suivi**				**Bilan à 8 semaines**	**Bilans de suivi après reprise**		
N° de visite	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Vn**
Date	**J0**	**J1**	**J15**	**J29**	**J43**	**Autour J50**	**J57**	**J71**	**Jn**
Consentement éclairé signé	**X**								
Critères d'inclusion / non inclusion	**X**								
Randomisation	**X**								
Examen clinique									
Poids	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Taille Surface.corporelle	**X**								
Etat général / OMS	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Traitements concomitants	**X**								
Toxicités (2)									
Evaluation de la tolérance			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Examen biologique (4)									
NFS, plaquettes	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TP,TCK	**X**								
Ionogramme, Ca	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Protidémie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Albuminémie, LDH	**X**								
Bilan hépatique	**X**		**X****	**X****	**X****	**X**	**Examen tous les deux mois**		
Creatininémie	**X**	**X**	**X**	**X**	**X**	**X**	**Examen tous les deux mois**		
Glycémie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
ACE, Ca 19-9 *	**X**					**X**	**Examen tous les deux mois**		
Test de grossesse	**X**(1)								
Bilan paraclinique(3)									
Scanner Thoracoabdominopelvien	**X**					**X**	**Examen scanographique tous les 2 mois**		
ECG	**X**								
Questionnaire de Qualité de Vie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

6 mois de traitement prévus pour le bras B

Plan de surveillance BRAS B GEMCITABINE													
Visite	**Bilan inclusion**	**Bilans de suivi**							**Bilan à 8 semaines**	**Bilans de suivi après reprise**			
N° de visite	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Vn**
Date	**J0**	**J1**	**J8**	**J15**	**J22**	**J29**	**J36**	**J43**	**Autour J50**	**J57**	**J64**	**J71**	**Jn**
Consentement éclairé signé	X												
Critères d'inclusion / non inclusion	X												
Randomisation	X												
Examen clinique	X												
Poids	X	X		X		X		X	X	X		X	
Taille Surface.corporelle	X												
Etat général / OMS	X	X		X		X		X	X	X		X	
Traitements concomitant	X												
Toxicités (2)													
Evaluation de la tolérance			X	X	X	X	X	X	X	X	X	X	X
Examen biologique (4)													
NFS, plaquettes	X	X	X	X	X	X	X	X	X	X	X	X	X
TP,TCK	X												
Ionogramme, Ca	X			X		X		X	X	X		X	
Protidémie	X								X				
Albuminémie, LDH	X												
Bilan hépatique	X			X		X		X	X	**Examen tous les deux mois**			
Créatininémie	X			X		X		X	X	**Examen tous les deux mois**			
Glycémie	X			X		X		X	X	X		X	
ACE, Ca 19-9*	X								X	**Examen tous les deux mois**			
Test de grossesse	X(1)												
Bilan paraclinique(3)													
Scanner Thoracoabdomino pelvien	X								X	**Examen scanographique tous les 2 mois**			
ECG	X												
Questionnaire de Qualité de Vie	X			X		X		X	X	X		X	

**seul le marqueur le plus performant sera dosé ultérieurement, choisir le marqueur qui a la valeur initiale la plus importante par rapport à la normale*

*** Bilan hépatique avec Bilirubine totale, libre et conjuguée doit être fait au moins tous les mois*

(1) pour les femmes en âge de procréer sans moyen contraceptif efficace

(2) Evénements Indésirables Graves (EIG) à déclarer dans les 48 heures au promoteur jusqu'à 30 jours après la fin de la dernière cure de chimiothérapie. Au delà de cette période seuls les EIG susceptibles d'être dus à la recherche seront déclarés au promoteur dès lors qu'aucune autre cause que la recherche ne peut raisonnablement être attribuée.

(3) Le bilan radiologique peut être effectué au cours des 3 semaines précédant l'inclusion.

(4) Le bilan biologique doit être effectué au plus tard dans la semaine précédant l'inclusion.

Les patients sans progression ayant eu les 6 mois de traitements seront suivis tous les 2 mois. Seront évalués la qualité de vie avec remise du questionnaire EORTC QLQ-C30 et la progression de la maladie, grâce à l'imagerie.

Les patients ayant progressé seront suivis tous les 6 mois jusqu'au décès. Seront évalués : les effets toxiques à long terme et la survie. Si un autre traitement est établi, il devra être rapporté.

ANNEXE 3 :
Evaluation de l'état général en fonction de l'échelle de l'ECOG ou de l'OMS

ETAT GENERAL ECOG-ZUBROD/OMS	ECHELLE
Activité normale, sans restriction.	**0**
Restreint pour des activités physiques importantes mais patient ambulatoire et capable de fournir un travail léger.	**1**
Ambulatoire et capable de se prendre en charge, mais incapable de fournir un travail pendant plus 50% de son temps.	**2**
Capacité de prise en charge propre beaucoup plus limitée. Passe plus de 50 % de son temps au lit ou dans une chaise.	**3**
Complètement grabataire. Incapable de se prendre en charge. Le patient reste totalement couché au lit ou sur une chaise.	**4**

ANNEXE 4 :
Classification des évaluations tumorales
Classification RECIST (JNCI, 2/2/2000)

1. Mesure des lésions tumorales

1.1 Définitions

Les lésions tumorales seront réparties en deux grandes catégories :

Lésions mesurables : lésions qui peuvent être mesurées avec précision dans au moins une dimension (le plus grand diamètre étant reporté) soit ≥ à 20 mm avec un scanner conventionnel soit ≥ à 10 mm avec un scanner spiralé.

Lésions non mesurables : toutes les autres lésions comprenant les petites lésions de plus grands diamètres < à 20 mm avec un scanner conventionnel ou < à 10 mm avec un scanner spiralé et les véritables lésions non mesurables.

Toutes les mesures doivent être reportées dans le système métrique en utilisant une règle ou les calipers. Les évaluations de départ doivent être réalisées avec un délai le plus court possible (sans excéder 4 semaines) par rapport au début du traitement.

Les lésions qui sont considérées comme véritablement non mesurables sont les suivantes :

- Lésions osseuses
- Atteinte méningée
- Ascite
- Epanchement pleural et/ou péricardique
- Sein inflammatoire
- Lymphangite cutanée et/ou pulmonaire
- Masses abdominales qui ne sont pas confirmées ou suivies par une technique d'imagerie
- Lésion kystique

Les lésions tumorales situées en territoire irradié peuvent être considérées comme mesurables ou non selon les conditions définies dans le protocole.

1.2 Méthodes de mesure

La méthode de mesure et la technique utilisées pour les mesures des lésions doivent être identiques au début de l'étude et pendant le suivi. Les évaluations par imagerie sont préférées aux évaluations cliniques quand les deux méthodes ont été utilisées pour déterminer l'activité anti-tumorale du traitement.

Lésions cliniques
Les lésions cliniques seront considérées comme mesurables lorsqu'elles sont superficielles (nodule cutané, ganglion lymphatique palpable). Pour les lésions cutanées, une documentation par photographie couleur comportant une règle pour évaluer la taille de la lésion est recommandée.

Radiographie pulmonaire
Les lésions visibles sur les radiographies pulmonaires sont considérées comme mesurables lorsqu'elles sont clairement identifiées et cernées par de l'air pulmonaire. Toutefois le scanner est préférable.

Scanner et IRM
Scanner et IRM sont actuellement les techniques les plus reproductibles pour mesurer les lésions cibles et évaluer une réponse. Scanner conventionnel et IRM sont réalisés avec des coupes jointives d'au moins 10 mm d'épaisseur. Les scanners spiralés doivent être réalisés en utilisant des coupes jointives de 5 mm.
Cela s'applique au thorax, abdomen et pelvis. Tête et cou et les extrémités nécessitent des protocoles spécifiques.

Echographie
Lorsque le but de l'étude est l'évaluation d'une réponse objective, l'échographie ne doit pas être utilisée pour mesurer les lésions tumorales qui ne sont pas cliniquement d'accès facile.
L'échographie peut être une alternative à l'examen clinique pour mesurer des ganglions superficiels palpables, des lésions sous-cutanées et des nodules thyroïdiens. L'échographie peut être utilisée pour confirmer une disparition complète de lésions superficielles évaluées par examen clinique.

Endoscopie, laparoscopie
L'utilisation de ces techniques pour évaluer une réponse objective n'est pas complètement validée. Leur utilisation dans ce contexte spécifique nécessite des équipements sophistiqués et un niveau d'expertise qui n'est disponible que dans quelques centres.
Leur utilisation pour évaluer des réponses objectives doit être restreinte à la validation d'études dans des centres de référence. Toutefois de telles techniques peuvent être utilisées pour confirmer une réponse totale sur le plan pathologique lorsque des biopsies sont réalisées.

Marqueurs tumoraux
Les marqueurs tumoraux ne peuvent être utilisés seuls pour évaluer une réponse.
Si les marqueurs sont initialement au-dessus de leur valeur normale, ils doivent se normaliser lorsque le patient est considéré en réponse complète et lorsque toutes les lésions tumorales ont disparu.
Des critères additionnels de standardisation de l'utilisation du PSA et du CA-125 sont actuellement en cours de validation et peuvent être utilisés dans les essais cliniques.

Cytologie et histologie
Dans de rares cas, ces techniques peuvent être utilisées pour différencier une réponse partielle et une réponse complète. Par exemple dans les tumeurs germinales où un résidu bénin peut persister.
La confirmation cytologique de l'origine néoplasique d'un épanchement qui apparaît ou s'aggrave durant le traitement est nécessaire pour différencier réponse, stabilité et progression tumorale lorsqu'une tumeur mesurable est un critère nécessaire pour apprécier la réponse tumorale (un épanchement peut être un effet secondaire du traitement).

2. Evaluation de la réponse tumorale

2.1 Evaluation à l'inclusion

- **Détermination de la réponse tumorale globale et des lésions mesurables**

Pour évaluer une réponse objective, il faut apprécier la masse tumorale au début et en faire des mesures comparatives dans le suivi.
Seuls les patients présentant une maladie mesurable à l'inclusion peuvent être inclus dans des protocoles où la réponse tumorale est le critère principal d'évaluation. Une maladie mesurable est définie par la présence d'au moins une lésion mesurable. Si la maladie mesurable se limite à une lésion unique, sa nature néoplasique doit être confirmée par cytologie/histologie.

- **Documentation des lésions cibles/non cibles à l'inclusion**

Toutes les lésions mesurables et jusqu'à un maximum de 5 lésions par organe et de 10 au total, représentatives de tous les organes atteints doivent être considérées comme des lésions cibles, être notées et mesurées à l'inclusion. Les lésions cibles doivent être sélectionnées en fonction de leur taille (plus grand diamètre) et de la possibilité d'être mesurées avec précision de façon reproductible (soit par imagerie soit cliniquement). La somme des plus grands diamètres de toutes les lésions cibles calculées à l'inclusion sera utilisée comme référence pour objectiver une réponse tumorale. Toutes les autres lésions ou sites de la maladie doivent être notés et identifiés comme lésions non cibles à l'inclusion. Il n'est pas nécessaire de les mesurer. Dans le suivi, elles seront notées présentes ou absentes.

2.2 Critères de réponse

- **Evaluation des lésions cibles**

Réponse complète (RC) : disparition de toutes les lésions cibles.
Réponse partielle (RP) : diminution d'au moins 30% de la somme des plus grands diamètres des lésions cibles par rapport à la somme des plus grands diamètres des lésions cibles à l'inclusion.
Progression (MP) : augmentation d'au moins 20% de la somme des plus grands diamètres des lésions cibles en prenant comme référence la plus petite valeur de la somme des plus grands diamètres reportés depuis le début du traitement ou bien apparition d'une ou de plusieurs nouvelles lésions.
Maladie stable (MS) : pas de diminution ou d'augmentation suffisante pour entrer dans le cadre d'une réponse partielle ou d'une progression en référence à la plus petite somme des plus grands diamètres depuis le début du traitement.

- **Evaluation des lésions non cibles**

Réponse complète : disparition de toutes les lésions non cibles et normalisation des marqueurs tumoraux.
Réponse incomplète et maladie stable : Persistance de une ou plusieurs lésions non cibles et/ou persistance des marqueurs tumoraux au-dessus des valeurs normales.
Progression : apparition de une ou plusieurs nouvelles lésions. Progression non équivoque des lésions non cibles existantes.

- **Evaluation de la meilleure réponse globale**

La meilleure réponse globale est la meilleure réponse enregistrée depuis le début du traitement jusqu'à l'apparition d'une récidive ou d'une progression (en prenant comme référence pour la progression la plus petite mesure rapportée depuis le début du traitement).

En général, la meilleure réponse du patient dépendra de l'ensemble des mesures et de la confirmation des critères définis dans le paragraphe 2.2.

Lésions cibles	Lésions non cibles	Nouvelles lésions	Réponse globale
RC	RC	non	RC
RC	Réponse incomplète et maladie stable	non	RP
RP	non - MP	non	RP
MS	non - MP	non	MS
Si une lésion cible ou non cible progresse ou s'il y a apparition d'une nouvelle lésion, l'évaluation de la réponse globale est la progression de la maladie.			

Les patients présentant une altération de l'état général nécessitant l'interruption du traitement sans progression objective évidente de la maladie, doivent à ce moment être notés détérioration symptomatique. Le maximum doit être fait pour objectiver la progression même après arrêt du traitement.

Dans certaines circonstances, il peut être difficile de distinguer une maladie résiduelle du tissu normal. Quand cette distinction intervient dans l'évaluation d'une réponse complète, il est recommandé d'explorer la lésion résiduelle par biopsie et/ou cytologie à l'aiguille avant de confirmer la réponse complète.

2.3 Confirmation de la mesure/ durée de la réponse

- **Confirmation**

Pour donner le statut de réponse partielle ou de réponse complète, les modifications de mesure des tumeurs doivent être confirmées par de nouvelles mesures 4 semaines au moins après que la première réponse ait été observée.

Dans le cas de maladie stable, les mesures ne peuvent répondre à ce critère qu'au moins une fois après l'entrée dans l'étude pendant un intervalle de temps minimum (en général pas moins de six à huit semaines).

- **Durée de la réponse globale**

La durée de la réponse globale est déterminée depuis le moment où une réponse complète / réponse partielle est obtenue (la première rapportée) jusqu'au moment où une récidive/progression est objectivement documentée.

La durée de la réponse complète est déterminée depuis le moment où la réponse complète est obtenue jusqu'au moment où une récidive objective est documentée.

- **Durée d'une maladie stable**

Une maladie stable est déterminée à partir du début du traitement jusqu'à ce qu'un critère de progression soit rencontré en prenant comme référence le plus petit total des mesures rapportées depuis le début du traitement.

La pertinence clinique de la durée d'une maladie stable varie selon les types de tumeur et leur grade. Toutefois, il est recommandé de spécifier dans le protocole l'intervalle de temps minimum requis entre deux mesures pour déterminer la stabilité de la maladie. Cet intervalle de temps doit prendre en compte le bénéfice clinique attendu qu'un tel statut peut apporter à la population étudiée.

2.4 Survie sans progression

Ce document concerne en premier lieu l'utilisation des réponses objectives. Dans certains cas (tumeurs cérébrales, essais de drogues anticancéreuses), l'évaluation de la réponse tumorale peut ne pas être la méthode optimale pour estimer l'activité potentielle anti-tumorale de nouveaux agents/régimes. Dans de tels cas, la survie sans progression peut être considérée comme une alternative valable pour fournir une estimation initiale de l'effet biologique de nouveaux agents qui peuvent agir par mécanisme non cytotoxique. Il est clair que dans un essai non contrôlé proposant d'utiliser la survie sans progression, il sera nécessaire de documenter avec prudence les données pour estimer la survie sans progression attendue en l'absence de traitement efficace. Il est aussi recommandé que l'analyse soit tout à fait prudente en fonction de la probabilité de confusion des biais concernant par exemple la sélection ou l'estimation. Des essais non contrôlés utilisant la survie sans progression comme objectif primaire doivent être envisagés sur la base du cas par cas et la méthodologie à appliquer doit être décrite parfaitement dans le protocole.

2.5 Comité de relecture

Pour les études où le taux de réponse est l'objectif primaire, il est fortement recommandé que toutes les réponses soient revues par un expert indépendant de l'étude. Une revue simultanée du dossier des patients et des images radiologiques est la meilleure approche.

ANNEXE 5 :
Extrait des critères de toxicité (CTC–NCI)
Version du 31/05/2003

ANNEXE 6 :
Formulaire de notification d'un événement indésirable grave

NOTIFICATION D'UN EVENEMENT INDESIRABLE GRAVE

A faxer à la pharmacovigilance du BECT n°+ 33 (0)1 44 23 55 70

beCT FNCLCC Centre d'Investigation Clinique en Cancérologie

N° EudraCT : ..... **N° Protocole :** ..... **Pays :** .....

❒ **Evénement Indésirable Grave ATTENDU**	❒ **Evénement Indésirable Grave INATTENDU**
❒ **Rapport initial** ❒ **Rapport de suivi n°:** |__|	**Centre investigateur :** .....

(1) Selon le RCP (Vidal) ou BI (version la plus récente)

1. INFORMATIONS PATIENT

N° inclusion : |__|	Nom (3 lettres) : |__|__|__|	Prénom (2 lettres) : |__|__|	Date de naissance : |__|__| / |__|__| / |__|__|__|__|
Sexe : ❒ F ❒ M	Poids (kg) : |__|__|__|	Taille (cm) : |__|__|__|	Bras de traitement : |__|

2. INFORMATIONS SUR L'EVENEMENT

Date de survenue événement : \|__\|__\| / \|__\|__\| / \|__\|__\| **Toxicité (grade NCI – CTC V3):** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Diagnostic ou principaux symptômes... .....

.....

3. TYPE D'EVENEMENT

❒ Décès ..... date \|__\|__\| / \|__\|__\| / \|__\|__\|

❒ Mise en jeu du pronostic vital

❒ Hospitalisation (> 24h) ou prolongation d'hospitalisation) date \|__\|__\| / \|__\|__\| / \|__\|__\|

❒ Médicalement significatif, préciser : .....

❒ Invalidité / Incapacité temporaire ou permanente

❒ Autre cancer : .....

❒ Anomalie congénitale ou malformation fœtale

4. EVOLUTION

❒ Evénement en cours

❒ Résolution sans séquelle, date \|__\|__\| / \|__\|__\| / \|__\|__\|

❒ Résolution avec séquelles, date \|__\|__\| / \|__\|__\| / \|__\|__\|

Nature des séquelles : .....

❒ Décès en relation avec l'événement

❒ Décès sans rapport avec l'événement

❒ Inconnu

Date de fin d'hospitalisation : \|__\|__\| / \|__\|__\| / \|__\|__\|

5. TRAITEMENTS

CHIMIOTHERAPIE, RADIOTHERAPIE..	VOIE	DATES		DOSES ET UNITES		IMPUTABILITE
		Dates de traitement avant apparition de l'événement		Dernière dose administrée	Dose cumulative depuis la 1ère administration	1 : Exclu 2 : Douteux 3 : Plausible 4 : Vraisemblable 5 : Très vraisemblable 6 : Ne peut conclure
1.		Du|__|__||__|__||__|__|	au|__|__||__|__||__|__|			|__|
2.		Du|__|__||__|__||__|__|	au|__|__||__|__||__|__|			|__|
3.		Du|__|__||__|__||__|__|	au|__|__||__|__||__|__|			|__|
4.		Du|__|__||__|__||__|__|	au|__|__||__|__||__|__|			|__|
5.		Du|__|__||__|__||__|__|	au|__|__||__|__||__|__|			|__|

Un ou des traitements ont-ils été arrêtés ?

❒ Oui N° \|__\| N° \|__\| N° \|__\| N° \|__\| N°\|__\| ❒ Non ❒ NA

Disparition de l'événement après arrêt d'un ou des produits ?

❒ Oui ❒ Non ❒ NA

Un ou des traitements ont-ils été réintroduits ?

❒ Oui N° \|__\| N° \|__\| N° \|__\| N° \|__\| N°\|__\| ❒ Non ❒ NA

Réapparition de l'événement après réintroduction ?

❒ Oui ❒ Non ❒ NA

6. IMPUTABILITE GLOBALE *(Selon vous, cet événement est plutôt lié)*

❒ au(x) traitement(s) de l'essai (*préciser le(s) nom(s) des traitements*).....	❒ à la progression de la maladie
❒ au protocole de l'essai	❒ autre(s) maladie(s) concomitante(s)
❒ autre(s) traitement(s) concomitant(s)	❒ autre(s) :.....

7. NOTIFICATEUR

Nom et fonction du notificateur :

Etablissement :
Adresse :
Tél. :
Fax :
E-mail :

Date \|__\|__\| / \|__\|__\| / \|__\|__\|

Signature de l'investigateur/co-investigateur

ANNEXE 6 bis:
Formulaire complémentaire d'information d'un EIG inattendu

COMPLEMENT D'INFORMATION
D'UN EVENEMENT INDESIRABLE GRAVE INATTENDU
A faxer à la pharmacovigilance du BECT n° + 33 (0)1 44 23 55 70

beCT FNCLCC Centre d'Investigati Clinique e Cancérolo

N° EudraCT : ..... **N° Protocole :** ..... **Pays :** .....

❒ Rapport de suivi n° : |__|

Centre investigateur : .....

(1) Selon le RCP (Vidal) ou BI (version la plus récente)

1. INFORMATIONS PATIENT

N° inclusion : |_____|	Nom (3 lettres) : |__|__|__|	Prénom (2 lettres) : |__|__|	Date de naissance : |__|__| / |__|__| / |__|__|__|__|
Sexe : ❒ F ❒ M	Poids (kg) : |_____|	Taille (cm) : |_____|	Bras de traitement : |____|

2. INFORMATIONS SUR L'EVENEMENT

Date de survenue événement : |__|__| / |__|__| / |__|__| **Toxicité (grade NCI – CTC V3):** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Diagnostic ou principaux symptômes.....

.....

3. NARRATIF

.....

.....

.....

4. ÉVOLUTION

❒ Evénement en cours
❒ Résolution sans séquelle, date |__|__| / |__|__| / |__|__|
❒ Résolution avec séquelles, date |__|__| / |__|__| / |__|__|
Nature des séquelles : .....
❒ Décès en relation avec l'événement
❒ Décès sans rapport avec l'événement
❒ Inconnu
Date de fin d'hospitalisation : |__|__| / |__|__| / |__|__|

5. TRAITEMENTS *(compléter le tableau ci-après en page 2/2)*

6. TRAITEMENT DE L'ÉVÉNEMENT INDÉSIRABLE

Traitement	Dose/Unité	Voie	Indication	Date début	Date fin	En cour
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒

7. MÉDICATION CONCOMITANTE PERTINENTE *(à l'exclusion de celle utilisée pour traiter l'événement)*

Traitement	Dose/Unité	Voie	Indication	Date début	Date fin	En cours	Relation causale	
							oui	non
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒	❒	❒
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒	❒	❒
.....			.....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	❒	❒	❒

8. ANTÉCÉDENTS MÉDICAUX PERTINENTS ET/OU MALADIE(S) CONCOMITANTE(S)

.....

.....

9. IMPUTABILITE GLOBALE *(Selon vous, cet événement est plutôt lié)*

❒ au(x) traitement(s) de l'essai (*préciser le(s) nom(s) des traitements*).....
❒ au protocole de l'essai
❒ autre(s) traitement(s) concomitant(s)
❒ à la progression de la maladie
❒ autre(s) maladie(s) concomitante(s)
❒ autre(s).....

10. NOTIFICATEUR

Nom et fonction du notificateur :

Etablissement :
Adresse :
Tél. :
Fax :
E-mail :

Date |__|__| / |__|__| / |__|__|

Signature de l'investigateur/co-investigateur

COMPLEMENT D'INFORMATION D'UN EVENEMENT INDESIRABLE GRAVE INATTENDU (page 2/2)

A faxer à la pharmacovigilance du BECT n° + 33 (0)1 44 23 55 70

N° Protocole : **N° EudraCT :** **N° Patient :**

5. TRAITEMENTS

	Voie	Dates		Doses et unites		Modifications de traitements	Traitements		
		Dates de traitement avant apparition de l'événement		Dernière dose administrée	Dose cumulative depuis la 1ère adm.	(1) Réduction de dose (2) Interruption temporaire (3) Interruption définitive	Disparition EI après arrêt traitement 1 : Oui 2 : Non 3 : NA	Réapparition EI après réintroduction 1 : Oui 2 : Non 3 : NA	Imputabilité : 1 : Exclu 2 : Douteux 3 : Plausible 4 : Vraisemblable 5 : Très vraisemblable 6 : Ne peut conclure
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	
… … … … … … … … …		Du	Au			Date	Date	Dose :	

ANNEXE 7 :
Formulaire d'information destiné au patient[(1)]

ETUDE RANDOMISEE DE PHASE II / III COMPARANT L'ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] A LA GEMCITABINE EN PREMIERE LIGNE DE CHIMIOTHERAPIE DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Promoteur : Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), 101 rue de Tolbiac, 75654 PARIS CEDEX 13
Investigateur Coordonnateur : Pr. Thierry CONROY, Département d'Oncologie Médicale, Centre Alexis Vautrin 6, avenue de Bourgogne, 54511 Vandoeuvre-lès-Nancy cedex

1. Quel est l'objectif de cette étude ?

Madame, Monsieur,

Votre médecin vous a informé que vous êtes atteint d'un cancer du pancréas qui nécessite un traitement. Il vous propose de participer à une étude dont le but est d'évaluer l'efficacité et la tolérance d'une chimiothérapie associant oxaliplatine, irinotecan et LV5FU (Folfirinox) par rapport à une chimiothérapie de référence par gemcitabine.

2. Combien de personnes participeront à cette étude ?

Cette étude nationale comparative de phase II est réalisée par plusieurs équipes de médecins en France. Elle doit inclure 88 patients sur une période de 2 ans. La moitié des patients recevront le traitement par l'association Folfirinox, l'autre moitié la gemcitabine. L'étude de phase III sera également réalisée par les mêmes médecins et inclura sur une période de 3 ans **360 patients**.

3. Quel est le déroulement de l'étude ?

Si vous acceptez de participer à cette étude, vous devrez être examiné par votre médecin et effectuer, une prise de sang, un scanner thoraco-abdominopelvien, un électrocardiogramme et compléter un questionnaire de qualité de vie. Après avoir réalisé ces examens et s'il n'y a pas de contre indication à l'un des traitements, vous recevrez l'un de ces traitements, le choix étant décidé par tirage au sort :

-Soit un traitement par **gemcitabine**, un médicament potentiellement efficace et bien toléré de chimiothérapie. Il s'agit d'un des traitements de référence de votre maladie.

-Soit un traitement plus nouveau, appelé **Folfirinox**, qui utilise des médicaments démontrés efficaces dans votre maladie, mais pas tous utilisés de façon courante. Ce traitement associe trois médicaments de chimiothérapie :

- l'association 5-fluorouracile (5FU) et acide folinique (LV5FU), traitement reconnu comme efficace dans votre maladie,
- l'irinotecan (Campto®) et l'oxaliplatine (Eloxatine®), médicaments de chimiothérapie commercialisés jusqu'ici que pour le traitement des cancers du gros intestin.

Cette association (Folfirinox) a déjà été administrée chez des patients atteints d'un cancer du pancréas et ce traitement a montré une efficacité encourageante.

L'attribution de l'une de ces options est déterminée par tirage au sort effectué par ordinateur central. Le médecin et le patient n'ont aucune influence sur l'attribution des traitements.

Traitement par Folfirinox :

L'oxaliplatine s'administre par voie intraveineuse sur une durée de deux heures en perfusion le premier jour du traitement. Elle sera suivie de l'administration simultanée de l'acide folinique en perfusion de deux heures et de l'irinotecan en perfusion de 1h30 à débuter immédiatement après la fin de la perfusion d'oxaliplatine.

Le 5-FU s'administre immédiatement après la fin de la perfusion d'acide folinique et consistera en une dose en intraveineuse sur 5 mn puis en une perfusion continue sur 46h.

Ce traitement sera renouvelé 14 jours plus tard et pour une durée maximale de 6 mois soit 12 cycles

Traitement par Gemcitabine :

La gemcitabine s'administre par voie intraveineuse le premier jour de traitement (J1) puis chaque semaine à J8, J15, J22, J29, J36, J43. Une cure dure 56 jours.
Cette administration sera ensuite reprise à J57 pendant 3 semaines sur 4, soit à J57, J64 et J71 et sera suivi d'une semaine de pause. Ce le même schéma (3 semaines sur 4) sera poursuivi pour une durée de 6 mois.

Avant chaque cycle de chimiothérapie un bilan biologique ainsi qu'un examen clinique seront réalisés afin de vérifier que vous tolérez bien le traitement. Tous les quinze jours avant la consultation, votre médecin vous demandera de remplir un questionnaire dit de « qualité de vie » pour savoir comment vous supportez les traitements et comment se passe votre vie au quotidien. Il faut environ dix minutes pour y répondre. Le remplissage de ce questionnaire est très important pour évaluer votre qualité de vie tout au long de votre maladie.

Un bilan à huit semaines vous sera fait. Votre médecin vous fera un examen clinique, un bilan biologique, un scanner et vous demandera de renseigner le questionnaire de qualité de vie.

Un scanner vous sera fait tous les deux mois à partir de l'inclusion. Votre participation à cette étude n'entraînera pas de contraintes supplémentaires.

A tout moment votre médecin pourra décider de suspendre le traitement si ce traitement ne s'avère pas efficace sur votre maladie, si les effets indésirables du traitement sont jugés trop dangereux pour vous, si de nouvelles informations concernant le traitement suggèrent une inefficacité ou un danger. Vous pouvez également choisir de vous retirer de l'essai à tout moment pour quelques raisons que ce soit sans qu'il n'y ait de préjudice pour la prise en charge de votre maladie. Dans les deux cas une thérapeutique vous serait proposée par l'équipe médicale qui vous prend en charge.

Le Folfirinox comme la gemcitabine peuvent être réalisés en ambulatoire

4. Quelle est la durée de participation du patient à l'étude ?

Dans tous les cas, deux mois de traitement par chimiothérapie sont initialement prévus puis, en fonction des résultats d'un bilan réalisé tous les deux mois et de la tolérance de votre traitement, vous serez suivi pendant les six mois, puis régulièrement pendant au moins 2 ans.

5. Quels sont les bénéfices attendus ?

Le but de cette étude est d'améliorer le traitement de votre maladie en évaluant l'efficacité et la tolérance de ces deux chimiothérapies.

Le bénéfice principal attendu est une réduction totale ou partielle du volume de vos lésions et une diminution des symptômes que vous ressentez. Le bénéfice pourrait être également une plus grande efficacité du traitement (plus longue durée sans évolution de la maladie) et/ou une toxicité moins importante.

6. Quels sont les risques possibles ?

Comme tous les médicaments de ce type, la chimiothérapie que vous allez recevoir peut être responsable d'effets secondaires indésirables. Ceux-ci sont connus par les médecins qui vous surveilleront et vous donneront soit des traitements préventifs (anti-nauséeux, anti-vomissements), soit des traitements curatifs. Signalez tout effet auprès de votre médecin.

- Des nausées et des vomissements transitoires seront atténués par la prescription d'anti-émétiques;
- Un risque d'infection par baisse du nombre de globules blancs sanguins, un risque accru d'hémorragies et donc d'apparition spontanée d'écchymoses ou d'hématomes, une anémie par baisse du nombre de globules rouges ainsi qu'une fatigue sont des événements assez fréquents : ils sont surveillés par des prises de sang régulières ;
- L'apparition d'une fièvre (température supérieure à 38°C) peut témoigner d'une infection sévère, notamment si elle est associée à une diarrhée. Une fièvre nécessite d'appeler votre médecin traitant qui prescrira une prise de sang,
- Des douleurs musculaires liées à l'administration de l'oxaliplatine, peuvent être cause de l'arrêt du traitement; en général, cette neurotoxicité disparaît en 6 à 8 mois .
- Avec l'oxaliplatine, une gêne à la perception fine peut gêner la vie quotidienne (bouton de chemise par exemple)et nécessiter une diminution du traitement.
- Une fatigue anormale, est également possible
- Pendant la perfusion d'irinotecan, vous pourrez ressentir une transpiration abondante, des crampes abdominales, une diarrhée, une augmentation de la salivation ou des troubles visuels. Lorsqu'ils apparaissent, ces symptômes sont en général modérés et sont traités efficacement par une injection d'atropine, si vous ne présentez pas de contre-indication à ce médicament. Si cette injection a été nécessaire, elle sera répétée à titre préventif lors des traitements suivants
- Pendant la perfusion d'oxaliplatine, il arrive très rarement une sensation de spasme dans la gorge. C'est une illusion liée à l'anesthésie de la gorge mais il n'y a aucun risque de troubles respiratoires. Cet évènement est bénin et disparaît tout seul. Cependant par la suite, il nécessitera d'allonger la perfusion d'oxaliplatine à 6 heures (au lieu de 2 heures).
- Une diarrhée qui, rarement, peut être sévère. Si c'est le cas, vous devrez prendre un traitement anti-diarrhéique, du Lopéramide, pour le traitement de cette diarrhée. En cas de diarrhée sévère et persistante, votre médecin y ajoutera des antibiotiques. Si la diarrhée persiste, il peut décider d'une éventuelle hospitalisation pour quelques jours. Une note spécifique de recommandations et une ordonnance de Lopéramide et d'antibiotiques vous sera remise à la sortie de l'hôpital. Il vous est demandé de lire attentivement et de suivre rigoureusement ces recommandations
- Une chute de cheveux peut se produire et vous pourrez avoir une prescription de perruque si vous le désirez. Il est également possible d'utiliser un casque réfrigérant, ce qui limite le risque de chute des cheveux.
- Des fourmillements des extrémités en touchant un objet froid pendant quelques jours. Il peut également arriver des crampes des mollets pendant un ou deux jours.
- Une fièvre modérée et un peu de douleurs dans les muscles dans la nuit qui suit la perfusion de gembitabine.
- Lors d'un traitement par Oxaliplatine et 5-FU, des élévations des enzymes du foie lors des examens sanguins de contrôle sont fréquemment constatés. Ces élévations sont généralement peu importantes et n'entraînent aucun symptôme. Dans quelques cas, des symptômes peuvent être associés avec ces élévations des enzymes du foie et consister en une jaunisse, une ascite (accumulation de liquide dans l'abdomen), ou une augmentation de volume du foie et/ou de la rate. Ces anomalies du foie et ces symptômes peuvent être liés à votre maladie ou, dans de rares cas, refléter un effet direct du traitement sur le tissu du foie, qui pourrait modifier les

vaisseaux sanguins dans le foie (maladie veino-occlusive). Pendant la durée de l'étude, la fonction de votre foie sera contrôlée de façon régulière par des examens sanguins et, si un mauvais fonctionnement du foie ou des symptômes sans rapport avec votre maladie venaient à survenir, des examens complémentaires vous seraient proposés.

- En cas d'anémie, votre médecin pourra vous prescrire un traitement par érythropoïétine (Aranesp). Dans la mesure où il a été observé chez certains patients traités par érythropoïétine une augmentation de fréquence d'accidents thromboemboliques notamment lorsque le taux d'hémoglobine est supérieur à 13 g/dl, une surveillance accrue de votre numération sanguine sera effectuée. D'autre part, comme avec tout facteur de croissance, on ne peut pas exclure totalement le risque de croissance tumorale avec les érythropoïétines.

Ces effets secondaires, dont nous tenons à vous donner le descriptif détaillé, sont généralement modérés et ne nécessitent pas, le plus souvent, l'arrêt du traitement. Le traitement sera adapté à votre susceptibilité individuelle. Informer impérativement votre médecin qui jugera avec vous de leur importance. En cas de toxicité importante, les doses des molécules pourront avoir leur posologie diminuée, retardée, voire supprimée.
Vous êtes en droit de demander à tout moment l'arrêt du traitement si vous le souhaitez.

Durant la chimiothérapie, il existe un risque important de malformation en cas de grossesse. Vous ou votre partenaire devez utiliser une contraception efficace pendant la période de chimiothérapie et dans les trois mois qui suivront. Avant de commencer le traitement, votre médecin s'assurera que vous disposez du meilleur moyen de contraception adapté à votre cas.

Il est important que vous informiez votre médecin de tout événement qui pourrait survenir entre deux traitements de chimiothérapie (cures), même si vous pensez que cet événement n'est pas relié au médicament administré. En particulier, vous devez informer votre médecin de toute diarrhée ou fièvre.

7. Quelles sont les alternatives de traitements ?

Ni la chirurgie ni la radiothérapie ne peuvent vous être proposés, sauf dans des cas très particuliers. Les rayons peuvent parfois aider à mieux contrôler les douleurs et la chirurgie est parfois nécessaire pour dériver les voies biliaires et le tube digestif dans certains cas. Le traitement habituel de votre maladie dans votre situation est une chimiothérapie en perfusion. L'alternative est le traitement uniquement de vos symptômes, sans y associer de chimiothérapie.

8. Quels sont vos droits en tant que participant à cette étude ?

Le promoteur de cet essai, la Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), a pris toutes les dispositions prévues par la loi pour la protection des personnes se prêtant à la recherche biomédicale (loi Huriet du 20/12/1988, modifiée). Le promoteur a également souscrit une assurance de recherche biomédicale, conformément à la législation en vigueur, auprès de la Société Gerling France (111-113 rue de Longchamp, 75016 Paris) par l'intermédiaire de la société de courtage d'assurances Biomedic Insure (73, rue du général Weygand, 56037 Vannes, tel. 02 97 69 19 19).
Les modalités de ce protocole ont été soumis à l'examen du Comité Consultatif de Protection des Personnes dans la recherche Biomédicale(CCPPRB) de Lorraine le 08 avril 2004 lequel a pour mission de vérifier si les conditions requises pour votre protection et le respect de vos droits ont été respectés.
Le CCPPRB de Lorraine a rendu un avis favorable le 18 mai 2004
De plus selon les dispositions de la loi du 4 mars 2002, vous serez informé des résultats globaux de l'essai par l'investigateur.
Ce protocole a été examiné par le Comité de Patients de la Ligue Nationale Contre le Cancer.

Votre dossier médical restera naturellement confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par les personnes dûment mandatées par l'organisateur de la recherche soumises au secret professionnel.

9. A qui devez-vous vous adresser en cas de questions ou de problèmes ?

En cas de problèmes ou de questions, vous pouvez, vous adresser aux personnes suivantes :

Vos contacts dans l'étude	Coordonnées du médecin traitant du patient
(titre, nom, prénom, adresse et téléphone) :	
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....

(1) toutes les pages doivent être paraphées par l'investigateur/co-investigateur et le patient

10. Quel est le calendrier de votre traitement et de vos examens ?

Plan de traitement													
Date	**J1**	**J8**	**J15**	**J22**	**J29**	**J36**	**J43**	**J50**	**J57**	**J64**	**J71**	**J78**	**Jn**
	C1		**C2**		**C3**		**C4**		**C5**		**C6**		**Cn**
Bras A : FOLFIRINOX	*oxaliplatine 85 mg/m² J1+ irinotecan 180 mg/m² J1+ acide folinique 400 mg/m² J1, 5-FU bolus 400 mg/m² J1, 5-FU continu 2,4 g/m² sur 46 heures J1/ J2 de chaque cycle*								*Reprise du traitement selon le schéma précédent, toutes les 2 semaines*				
Bras B : gemcitabine	↑	↑	↑	↑	↑	↑	↑		↑	↑	↑		↑
	gemcitabine 1000 mg/m² de chaque semaine pendant 7 semaines								*Reprise de la gemcitabine 3 semaines sur 4*				

12 cycles prévus pour le bras A = 6 mois de traitement

Plan de surveillance BRAS A Folfirinox									
Visite	**Bilan inclusion**	**Bilans de suivi**				**Bilan à 8 semaines**	**Bilans de suivi après reprise**		
N° de visite	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Vn**
Date	**J0**	**J1**	**J15**	**J29**	**J43**	**Autour J50**	**J57**	**J71**	**Jn**
Consentement éclairé signé	**X**								
Critères d'inclusion / non inclusion	**X**								
Randomisation	**X**								
Examen clinique									
Poids	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Taille Surface.corporelle	**X**								
Etat général / OMS	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Traitements concomitants	**X**								
Toxicités (2)									
Evaluation de la tolérance			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Examen biologique (4)									
NFS, plaquettes	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TP,TCK	**X**								
Ionogramme, Ca	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Protidémie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Albuminémie, LDH	**X**								
Bilan hépatique	**X**		**X****	**X****	**X****	**X**	**Examen tous les deux mois**		
Creatininémie	**X**	**X**	**X**	**X**	**X**	**X**	**Examen tous les deux mois**		
Glycémie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
ACE, Ca 19-9 *	**X**					**X**	**Examen tous les deux mois**		
Test de grossesse	**X**(1)								
Bilan paraclinique(3)									
Scanner Thoracoabdominopelvien	**X**					**X**	**Examen scanographique tous les 2 mois**		
ECG	**X**								
Questionnaire de Qualité de Vie	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

6 mois de traitement prévus pour le bras B

Plan de surveillance BRAS B GEMCITABINE													
Visite	**Bilan inclusion**	**Bilans de suivi**							**Bilan à 8 semaines**	**Bilans de suivi après reprise**			
N°de visite	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Vn**
Date	**J0**	**J1**	**J8**	**J15**	**J22**	**J29**	**J36**	**J43**	**Autour J50**	**J57**	**J64**	**J71**	**Jn**
Consentement éclairé signé	X												
Critères d'inclusion / non inclusion	X												
Randomisation	X												
Examen clinique	X												
Poids	X	X		X		X		X	X	X		X	
Taille Surface.corporelle	X												
Etat général / OMS	X	X		X		X		X	X	X		X	
Traitements concomitant	X												
Toxicités (2)													
Evaluation de la tolérance			X	X	X	X	X	X	X	X	X	X	X
Examen biologique (4)													
NFS, plaquettes	X	X	X	X	X	X	X	X	X	X	X	X	X
TP,TCK	X												
Ionogramme, Ca	X			X		X		X	X	X		X	
Protidémie	X								X				
Albuminémie, LDH	X												
Bilan hépatique	X			X		X		X	X	**Examen tous les deux mois**			
Créatininémie	X			X		X		X	X	**Examen tous les deux mois**			
Glycémie	X			X		X		X	X	X		X	
ACE, Ca 19-9*	X								X	**Examen tous les deux mois**			
Test de grossesse	X(1)												
Bilan paraclinique(3)													
Scanner Thoracoabdomino pelvien	X								X	**Examen scanographique tous les 2 mois**			
ECG	X												
Questionnaire de Qualité de Vie	X			X		X		X	X	X		X	

**seul le marqueur le plus performant sera dosé ultérieurement, choisir le marqueur qui a la valeur initiale la plus importante par rapport à la normale*

*** Bilan hépatique avec Bilirubine totale, libre et conjuguée doit être fait au moins tous les mois*

(1) pour les femmes en âge de procréer sans moyen contraceptif efficace

(2) Evénements Indésirables Graves (EIG) à déclarer dans les 48 heures au promoteur jusqu'à 30 jours après la fin de la dernière cure de chimiothérapie. Au delà de cette période seuls les EIG susceptibles d'être dus à la recherche seront déclarés au promoteur dès lors qu'aucune autre cause que la recherche ne peut raisonnablement être attribuée.

(3) Le bilan radiologique peut être effectué au cours des 3 semaines précédant l'inclusion.

(4) Le bilan biologique doit être effectué au plus tard dans la semaine précédant l'inclusion.

ANNEXE 7 :
Formulaire de consentement de participation du patient[(1)]

ETUDE RANDOMISEE DE PHASE II COMPARANT L'ASSOCIATION [OXALIPLATINE / IRINOTECAN / LV5FU (FOLFIRINOX)] A LA GEMCITABINE SEULE EN PREMIERE LIGNE DE TRAITEMENT DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Je soussigné(e) :

Nom :.....Prénom :.....

Adresse :.....

CONSENS EXPRESSEMENT A PARTICIPER A CETTE RECHERCHE DANS LES CONDITIONS QUI M'ONT ETE PRECISEES DANS LA FICHE D'INFORMATION.

J'ai reçu et j'ai bien compris les informations qui m'ont été remises par le Dr ..... qui m'a expliqué l'objectif, le déroulement, et la durée de cette recherche, ainsi que les bénéfices attendus et les risques éventuels, et qui m'a précisé que je suis libre d'accepter ou de refuser.

Mon consentement ne décharge par les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Si je le désire, je serai libre à tout moment d'arrêter ma participation. J'en informerai alors le Dr ..... Il me proposera, si je le souhaite un autre traitement.

Dans le cadre d'éventuelles publications scientifiques, seules les informations ne faisant mention, ni de mon nom, ni de mon adresse, peuvent être utilisées. Les données qui me concernent resteront strictement confidentielles et je n'autorise leur consultation que par des personnes mandatées par l'organisateur de la recherche ou par un représentant des Autorités de Santé.

J'accepte également que les données enregistrées à l'occasion de cet essai puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte conformément à la loi Informatique et Liberté du 6/1/1978 modifiée par les lois n°94-548 du 1/7/1994 et n° 2002-303 du 4/3/2002. J'ai bien noté que le droit d'accès (articles 34 et 40 modifié) et de rectification (article 36), que m'ouvrent les textes susvisés, pourra s'exercer à tout moment auprès du Dr.....et que les données me concernant pourront m'être communiquées ou par l'intermédiaire d'un médecin de mon choix.

Nom du patient ou de son représentant légal	Date	Signature
Nom du médecin investigateur ou du médecin qui le représente (co-investigateur) :	Date	Signature

(1) (toutes les pages doivent être paraphées, un exemplaire cosigné doit être remis à la personne qui participe à la recherche)

ANNEXE 8 :
Conseils pour l'utilisation du questionnaire EORTC QLQ-30 pour mesurer la qualité de vie

1 – PASSATION DU QUESTIONNAIRE

- Fournir un environnement calme et confortable pour le remplissage du questionnaire.
- Remettre le questionnaire au malade en personne en pensant à emporter un stylo bille supplémentaire (le patient peut ne pas avoir de stylo avec lui).
- Prévoir une aide par une personne désignée (par exemple infirmière, assistante, technicienne de recherche clinique, secrétaire) au cas où le malade ait besoin d'explications.
- Expliquer verbalement les instructions ou les questions si celles-ci ne paraissent pas claires sans influencer les réponses. Lui montrer comment entourer (et non cocher) les réponses.
- Parfois remplir à la place du patient en lui posant les questions (patients âgés, fatigués ou ayant oublié ses lunettes ...) et alors le mentionner.
- Vérifier lors de la récupération du questionnaire que les données non remplies le sont délibérément et ne résultent pas d'un oubli.
- Noter la cause du refus si le patient refuse de remplir l'ensemble du questionnaire.

2 – MOMENT DE REMISE DU QUESTIONNAIRE

a – Avant l'inclusion

- Le patient doit être au courant de sa situation avant le remplissage du questionnaire de qualité de vie.
- Le médecin doit avoir expliqué le but du questionnaire.
- Faire remplir le questionnaire avant randomisation pour que l'issue de la randomisation n'influe pas les résultats de qualité de vie.
- Le remplissage du questionnaire sera un critère d'inclusion, car disposer du questionnaire avant traitement permettra de détecter un biais de sélection si le suivi ultérieur vient à manquer (patients avec une qualité de vie médiocre à l'inclusion auxquels on n'ose plus ensuite présenter un questionnaire car la QdV s'est encore dégradée).

b – Avant chaque cure

- Le questionnaire est considéré comme acceptable s'il est rempli le jour du traitement ou dans les 3 jours qui précèdent celui-ci. Le remplissage par téléphone est déconseillé.
- Si le traitement est reporté, le remplissage du questionnaire le sera également.

c – A chaque remise de questionnaire

- Le questionnaire est remis au malade et rempli préférentiellement avant que celui-ci ait vu le médecin, à la fois pour réduire les biais liés au dialogue avec le médecin ou ceux dus aux résultats du traitement et aussi pour permettre au patient de discuter avec le médecin des symptômes ou des domaines de qualité de vie réduite.
- Déconseiller d'emmener le questionnaire à la maison car il n'y aura aucun contrôle sur le jour où le questionnaire sera rempli réellement et les réponses au questionnaire seront influencées par la famille ou les amis.
- En cas de symptômes sévères décrits sur le questionnaire de qualité de vie, la personne qui récupère le questionnaire peut rappeler au patient qu'il doit signaler les problèmes au médecin responsable de sa chimiothérapie.
- Il faut remettre le questionnaire à chaque cure prévue et aussi à la sortie d'étude, même si le patient ne va pas bien (c'est précisément à ce moment-là qu'il est intéressant d'étudier les altérations de la qualité de vie et qu'il est important de tenter de les corriger).

3 – ORGANISATION INTERNE DE CHAQUE CENTRE

- Nommer dans chaque centre un responsable de la remise des questionnaires et prévoir son remplacement en cas d'absence ou de vacances.
- Prévoir un échéancier de remise des questionnaires en même temps que la randomisation dans l'étude, en remettre un double au patient et le lui expliquer.
- Chaque centre gardera une copie des questionnaires avant de les envoyer avec les fiches de l'étude.
- Mettre un double du résumé du protocole dans chaque dossier et rendre accessible le protocole complet dans chaque secteur de soins.

ANNEXE 9 :
EORTC QLQ-C30 (version 3.0)

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions ***en entourant le chiffre*** qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
1. Avez-vous des difficultés à faire certains efforts physiques pénibles, comme porter un sac à provision chargé ou une valise ?	1	2	3	4
2. Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
3. Avez-vous des difficultés à faire un petit tour dehors ?	1	2	3	4
4. Etes-vous obligé(e) de rester au lit ou dans un fauteuil pendant la journée ?	1	2	3	4
5. Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux W.C ?	1	2	3	4

AU COURS DE LA SEMAINE PASSEE :

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
6. Avez-vous été gêné(e) pour faire votre travail ou vos activités de tous les jours ?	1	2	3	4
7. Avez-vous été gêné(e) dans vos activités de loisirs ?	1	2	3	4
8. Avez-vous eu le souffle court ?	1	2	3	4
9. Avez-vous eu mal ?	1	2	3	4
10. Avez-vous eu besoin de repos ?	1	2	3	4
11. Avez-vous eu des difficultés pour dormir ?	1	2	3	4
12. Vous êtes-vous senti(e) faible ?	1	2	3	4
13. Avez-vous manqué d'appétit ?	1	2	3	4
14. Avez-vous eu des nausées (mal au cœur) ?	1	2	3	4
15. Avez-vous vomi ?	1	2	3	4
16. Avez-vous été constipé(e) ?	1	2	3	4
17. Avez-vous eu de la diarrhée ?	1	2	3	4
18. Etiez-vous fatigué(e) ?	1	2	3	4

AU COURS DE LA SEMAINE PASSEE :

	Pas du tout	Un peu	Assez	Beaucoup
19. Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses, par exemple, pour lire le journal ou regarder la télévision ?	1	2	3	4
21. Vous êtes-vous senti(e) tendu(e) ?	1	2	3	4
22. Vous êtes-vous fait du souci ?	1	2	3	4
23. Vous êtes-vous senti(e) irritable ?	1	2	3	4
24. Vous êtes-vous senti(e) déprimé(e) ?	1	2	3	4
25. Avez-vous eu des difficultés pour vous souvenir de certaines choses ?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans votre vie familiale ?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans vos activités sociales (par exemple sortir avec des amis, aller au cinéma ...) ?	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers ?	1	2	3	4

Pour les deux questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						**Excellent**

30.Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						**Excellent**

ANNEXE 10 :
recommandations pour l'utilisation du filgrastim : (NEUPOGEN®)

ADMINISTRATION / POSOLOGIE :

La dose recommandée de NEUPOGEN est de 0,5 MU (5 µg)/kg/jour. La première injection de NEUPOGEN doit être effectuée au plus tôt 24 heures après la fin de la chimiothérapie cytotoxique. NEUPOGEN doit être administré de façon quotidienne par voie sous-cutanée ou en perfusion intraveineuse de 30 minutes, la solution de NEUPOGEN étant alors diluée dans une solution de glucose à 5% (pour une information complète concernant la dilution, consulter le dictionnaire VIDAL).
La préférence doit être donnée à la voie sous-cutanée dans la majorité des cas.
L'administration quotidienne de NEUPOGEN doit être poursuivi jusqu'à ce que le nadir du nombre de neutrophiles soit dépassé et que ce nombre soit revenu à une valeur normale.

MISES EN GARDE SPECIALES :

Chez les patients cancéreux : Leucocytose : Réaliser une numération leucocytaire à intervales réguliers. Arrêt du traitement si le nombre de leucocytes dépasse $50x10^9$/l après la date attendue du nadiraprès une chimiothérapie ou arrêt ou diminution de la posologie si le taux de leucocytes dépasse $70x10^{9/l}$ lors d'une collection de cellules souches.

Risques associés à la chimiothérapie intensive : Pas d'action sur la thrombopénie, ni sur l'anémie dues à la chimiothérapie cytotoxique. Surveiller le nombre de plaquettes et l'hématocrite.

Autres précautions : Prudence en cas d'intolérance héréditaire au fructose.

INTERACTIONS *:

Administration non recommandée dans les 24 heures précédent ou suivant une chimiothérapie myélosuppressive.

CONTRE-INDICATIONS :

NEUPOGEN ne doit pas être administré aux patients présentant une hypersensibilité connue au produit ou à l'un de ses constituants. NEUPOGEN ne doit pas être administré pour augmenter les doses de chimiothérapie cytotoxique au-delà des dosages établis. NEUPOGEN ne doit pas être administré à des patients présentant une neutropénie congénitale sévère (syndrome de Kostmann) avec anomalies cytogénétiques

GROSSESSE ET ALLAITEMENT *:

Innocuité non établie.

EFFET INDESIRABLE *:

Chez les patients atteint de cancer : Le plus fréquent : douleurs osseuses, troubles urimaires, modifications biologiques légères ou modérées, dose-dépendantes et réversibles à l'arrêt du traitement (élévation de gamma GT, élévation des Phosphatases Alcalines, élévation du taux de LDH).
Dans de rares cas : Baisses transitoires de la pression artérielles, perturbations vasculaires, vascularités cutanées, syndrome de Sweet (dermatose fébrile aiguë), poussées de polyarthrite rhumatoïde, syndrome de détresse respiratoire de l'adulte et réaction allergique.

INCOMPATIBILITES *: Solutions salines

*** pour une information complète, consulter le dictionnaire VIDAL**

ANNEXE 11 :
recommandations pour l'utilisation de la darbepoetin alfa (ARANESP®)

ADMINISTRATION / POSOLOGIE :

L'Aranesp®sera administré en sous cutané à une dose initiale de 6,75 µg/kg, une fois toutes les 3 semaine, chez les patients présentant une anémie (par ex. taux d'hémoglobine ≤ 11 g/dl (6,8 mmol/l)). Le taux cible d'hémoglobine à atteindre pour corriger l'anémie et réduire les besoins transfusionnels est de 12,0 g/dl ou 7,5 mmol/l.

- Si le taux d'hémoglobine dépasse 14,0 g/dl ou 8,7 mmol/l, le traitement doit être interrompu *(voir infra, § 2)*.
- Si la réponse clinique (fatigue, taux d'hémoglobine) n'est pas satisfaisante après 9 semaines (3 injections), arrêt de l'Aranesp® .

Les indications transfusionnelles sont laissées au libre choix de clinicien.

Ne pas oublier de faire une supplémentation en fer si le taux de ferritine sérique est < 100 µg/l ou si le coefficient de saturation de la transferrine est <20 %)

Le traitement par Aranesp® doit être poursuivi au moins pendant 4 semaines après l'arrêt de la chimiothérapie, ou jusqu'à ce que le taux d'hémoglobine se soit normalisé à une valeur supérieure ou égale à 12,0 g/dl ou 7,5 mmol/l. Une mesure de la NFS sera effectuée de façon hebdomadaire.

CONDUITE A TENIR :

1) **En cas d'événement indésirable grave** : A n'importe quel moment de l'étude, tout événement indésirable grave qui serait considéré par l'investigateur comme lié au traitement par Aranesp® entraînera l'arrêt immédiat du traitement. Suite à cela, un suivi régulier du patient sera assuré jusqu'à la disparition ou la stabilisation de cet événement.

Il est recommandé de ne pas administrer l'Aranesp® si le taux d'hémoglobine est > à 11 g/dL. Il est nécessaire de veiller à ce que ce taux ne dépasse pas 13g/dL. En cas d'augmentation de taux d'hémoglobine de plus de 2 g/dL en quatre semaines, réduire la posologie de 25 à 50 %.

ANNEXE 12 :
Liste des EIG attendus

Extrait du RCP oxaliplatine - ELOXATINE®

DC/EFFETS INDÉSIRABLES
Les effets indésirables rapportés lors du développement clinique de l'oxaliplatine dans le traitement du cancer colorectal métastatique ont été analysés sur une population de 244 patients traités en monothérapie et près de 1500 patients traités en association avec le 5-fluorouracile.

- **Système hématopoïétique :**

L'oxaliplatine administré en monothérapie (130 mg/m ^{2} toutes les 3 semaines) entraîne peu de toxicité hématologique de grades 3 et 4.

Oxaliplatine seul	Tous grades	Grade 3	Grade 4
Anémie (% patients)	64	3	< 1
Neutropénie (% patients)	15	2	< 1
Thrombopénie (% patients)	41	2	< 1

Lorsque l'oxaliplatine est utilisé en association avec le 5-fluorouracile et l'acide folinique, l'incidence des neutropénies et des thrombopénies est supérieure à celle observée avec l'association 5-fluorouracile/acide folinique seule.

Oxaliplatine associé au 5-fluorouracile	85 mg/m ^{2} toutes les 2 sem		
	Tous grades	Grade 3	Grade 4
Anémie (% patients)	83	4	< 1
Neutropénie (% patients)	66	25	13
Thrombopénie (% patients)	76	3	< 1

- Système digestif :

En monothérapie, l'oxaliplatine (130 mg/m ^{2} toutes les 3 semaines) peut entraîner une anorexie, des nausées, des vomissements, des diarrhées et des douleurs abdominales, non sévères dans la majorité des cas.

Oxaliplatine seul	Tous grades	Grade 3	Grade 4
Nausées, vomissements (% patients)	69	12	2
Diarrhées (% patients)	41	4	< 1
Mucites (% patients)	4	< 1	< 1
Anomalies hépatiques (% patients)	46	10	2

Un traitement préventif et/ou curatif avec des agents antiémétiques puissants est indiqué. Lorsque l'oxaliplatine est associé avec le 5-fluorouracile (avec ou sans acide folinique), la fréquence, comme la sévérité, des diarrhées et des mucites est augmentée de façon significative comparativement à celle observée avec le 5-fluorouracile seul.
De rares cas de colites, incluant des diarrhées à Clostridium difficile ont été rapportés. Une déshydratation, un iléus paralytique, une occlusion intestinale, une hypokaliémie, une acidose métabolique et une altération de la fonction rénale peuvent être provoqués par des diarrhées et/ou des vomissements sévères, notamment lorsque l'oxaliplatine est associé au 5-fluorouracile (cf Mises en garde/Précautions d'emploi).

Oxaliplatine associé au 5-fluorouracile	85 mg/m ^{2} toutes les 2 sem		
	Tous grades	Grade 3	Grade 4
Nausées, vomissements (% patients)	71	11	1
Diarrhées (% patients)	58	7	3
Mucites (% patients)	42	7	1

Des élévations des enzymes hépatiques de grades 1 et 2 sont fréquentes lors du traitement par oxaliplatine. Dans les études randomisées comparant l'association 5-fluorouracile/acide folinique à l'association 5-fluorouracile/acide folinique/oxaliplatine, l'incidence des élévations des enzymes hépatiques de grades 3 et 4 est comparable dans les deux groupes.

- Système nerveux :

La toxicité limitante de l'oxaliplatine est neurologique. Il s'agit essentiellement d'une neuropathie périphérique sensitive caractérisée par des dysesthésies et/ou des paresthésies des extrémités, accompagnées ou non de crampes, souvent déclenchées par le froid. Ces symptômes apparaissent chez 85 à 95 % des patients traités. La durée de ces symptômes, généralement régressifs entre les cycles de traitement, s'accroît avec la répétition de ceux-ci.

La survenue de douleurs et/ou d'une gêne fonctionnelle nécessite, selon la durée des symptômes, l'ajustement de la dose, voire l'arrêt du traitement (cf Mises en garde/Précautions d'emploi).
Cette gêne fonctionnelle, qui comprend des difficultés lors de l'exécution des gestes fins, est une conséquence possible de l'atteinte sensitive. Le risque de survenue d'une gêne fonctionnelle pour une dose cumulée d'environ 800 mg/m ^{2} (soit 10 cycles) est de 15 % ou moins. La symptomatologie neurologique s'améliore le plus souvent à l'arrêt du traitement.
Des manifestations neurosensorielles aiguës ont été rapportées (cf Sécurité préclinique). Elles débutent dans les heures suivant l'administration et surviennent souvent lors d'une exposition au froid. Elles se caractérisent par des paresthésies transitoires, des dysesthésies ou hypoesthésies, voire par un syndrome aigu de dysesthésie pharyngolaryngée. Ce syndrome aigu, dont l'incidence est estimée entre 1 % et 2 %, se caractérise par des sensations subjectives de dysphagie ou de dyspnée sans signe objectif de détresse respiratoire (sans cyanose, ni hypoxie) ou par laryngospasme ou bronchospasmes (sans stridor ou sifflement) ; une contracture de la mâchoire, une dysesthésie linguale, une dysarthrie et une oppression thoracique ont également été observées.
Bien que des antihistaminiques et des bronchodilatateurs aient été administrés dans ces situations, cette symptomatologie est rapidement réversible, même en l'absence de tout traitement. L'allongement de la durée de la perfusion dans les cycles suivants favorise la diminution de l'incidence de ce syndrome (cf Mises en garde/Précautions d'emploi).
D'autres symptômes neurologiques, comme une dysarthrie, la disparition des réflexes ostéotendineux et un signe de Lhermitte, ont été rapportés lors de traitement par oxaliplatine. Des cas isolés de névrites optiques ont été rapportés.

- Réactions allergiques :

Des réactions anaphylactiques peu fréquentes (en monothérapie) ou fréquentes (en association avec le 5-fluorouracile ± acide folinique) ont été rapportées incluant des cas de bronchospasme, d'angiœdème, d'hypotension et de choc anaphylactique.

Des cas fréquents de réactions allergiques tels que rash cutané (en particulier urticaire), conjonctivite, rhinite ont été rapportés.

- Autres effets :

Une ototoxicité clinique est survenue chez moins de 1 % des patients traités par oxaliplatine. De rares cas de surdité ont été rapportés.
Des anomalies de la fonction rénale ont été rapportées chez environ 3 % des patients traités, des anomalies de grades 3 et 4 chez moins de 1 % des patients.
Lors des études cliniques, ainsi que depuis sa mise sur le marché, aucune arythmie ventriculaire significative n'a été rapportée lors d'administration d'oxaliplatine.
Des cas très fréquents de fièvre ont été rapportés : soit des fièvres isolées de type immunologique soit des fièvres d'origine infectieuse (associées ou non à une neutropénie).
De rares cas de thrombocytopénies immunoallergiques et d'anémies hémolytiques immunoallergiques ont été rapportées.
De rares cas de pneumopathies interstitielles aiguës et de fibroses pulmonaires ont été rapportés (cf Mises en garde/Précautions d'emploi).
Une alopécie modérée a été rapportée chez 2 % des patients traités par l'oxaliplatine seul ; l'association de l'oxaliplatine et du 5-fluorouracile n'augmente pas l'incidence des alopécies observées lors des traitements par le 5-fluorouracile seul.
L'extravasation peut provoquer une douleur locale ainsi qu'une inflammation, pouvant être sévère et entraîner des complications, particulièrement lorsque l'oxaliplatine est perfusé par voie veineuse périphérique (cf Mises en garde/Précautions d'emploi).
Une baisse transitoire de l'acuité visuelle a été rapportée chez moins de 0,1 % des patients à la suite d'une administration d'oxaliplatine.
Des dysarthries ont été rapportées rarement (cf supra : système nerveux).

Extrait du RCP irinotécan- CAMPTO®

DC/EFFETS INDÉSIRABLES

Les effets indésirables suivants, possiblement ou probablement liés à l'administration de Campto, ont été analysés sur une population de 765 patients à la dose recommandée de 350 mg/m ^{2} en monothérapie, et de 145 patients traités par Campto en association avec 5-FU/AF toutes les 2 semaines à la dose recommandée de 180 mg/m ^{2}.

Effets gastro-intestinaux :

- Diarrhée tardive :

  La diarrhée tardive (survenant plus de 24 heures après l'administration de Campto) constitue une toxicité dose-limitante de Campto.

  - En monothérapie : La diarrhée sévère est observée chez 20 % des patients qui ont suivi les recommandations de prise en charge de la diarrhée. Une diarrhée sévère est retrouvée dans 14 % des cycles évaluables.Le délai médian d'apparition de la première selle liquide est de 5 jours après la perfusion de Campto.
  - En association : Une diarrhée sévère est observée chez 13,1 % des patients qui ont suivi les recommandations de prise en charge de la diarrhée. Une diarrhée sévère est retrouvée dans 3,9 % des cycles évaluables.

  De rares cas de colite pseudomembraneuse ont été rapportés, dont un cas avec une documentation bactériologique (Clostridium difficile).

- Nausées et vomissements :
  - En monothérapie : Des nausées et vomissements sévères sont observés chez environ 10 % des patients ayant reçu un traitement antiémétique.
  - En association : Une incidence moindre des nausées et vomissements sévères est observée (respectivement 2,1 % et 2,8 % des patients).

- Déshydratation : des épisodes de déshydratation généralement associés à une diarrhée et/ou des vomissements sont rapportés. De rares cas d'insuffisance rénale, d'hypotension ou de collapsus

cardiovasculaire ont été observés chez des patients ayant présenté des épisodes de déshydratation associés à une diarrhée et/ou à des vomissements.

- Autres événements gastro-intestinaux : Une constipation relative à Campto et/ou au lopéramide a été observée en monothérapie chez moins de 10 % des patients et, en association, chez 3,4 % des patients traités. De rares cas d'occlusion intestinale, d'iléus ou d'hémorragie gastro-intestinale, et de rares cas de colites, incluant des typhlites, des colites ischémiques et ulcéreuses ont été rapportés. De rares cas de perforations intestinales sont rapportés. D'autres effets peu sévères incluant anorexie, douleurs abdominales et stomatite ont été également observés.

Hématologie :

La neutropénie constitue une toxicité dose-limitante. La neutropénie était réversible et non cumulative ; le délai médian d'apparition du nadir était de 8 jours, que ce soit en monothérapie ou en association.

- En monothérapie :La neutropénie est observée chez 78,7 % des patients et est sévère (nombre de neutrophiles < 500/mm ^{3}) dans 22,6 % des cas. Parmi les cycles évaluables, 18 % se compliquent d'une neutropénie < 1000/mm ^{3}, dont 7,6 % d'une neutropénie < 500/mm ^{3}.La récupération totale est en général atteinte le 22 ^{e} jour. Une fièvre accompagnée d'une neutropénie sévère est rapportée chez 6,2 % des patients et dans 1,7 % des cycles. Des épisodes infectieux sont survenus chez environ 10,3 % des patients (2,5 % des cycles), ont été associés à une neutropénie sévère chez environ 5,3 % des patients (1,1 % des cycles), et ont entraîné 2 décès. Une anémie a été rapportée chez environ 58,7 % des patients (8 % avec une hémoglobine < 8 g/dl et 0,9 % avec une hémoglobine < 6,5 g/dl).Une thrombocytopénie (< 100 000/mm ^{3}) a été observée chez 7,4 % des patients et 1,8 % des cycles, dont 0,9 % des patients avec des plaquettes ≤50 000/mm ^{3}, soit 0,2 % des cycles. Presque tous les patients ont normalisé leur numération plaquettaire le 22 ^{e} jour.

- En association :Une neutropénie est observée chez 82,5 % des patients et est sévère (nombre de neutrophiles < 500/mm ^{3}) dans 9,8 % des cas. Parmi les cycles évaluables, 67,3 % se compliquent d'une neutropénie < 1000/mm ^{3}, dont 2,7 % d'une neutropénie < 500/mm ^{3}.La récupération totale est en général atteinte dans les 7 à 8 jours. Une fièvre accompagnée d'une neutropénie sévère est rapportée chez 3,4 % des patients et dans 0,9 % des cycles. Des épisodes infectieux sont survenus chez environ 2 % des patients (0,5 % des cycles), ont été associés à une neutropénie sévère chez environ 2,1 % des patients (0,5 % des cycles), et ont entraîné 1 décès. Une anémie est rapportée chez environ 97,2 % des patients (2,1 % avec une hémoglobine < 8 g/dl).Une thrombocytopénie (< 100 000/mm ^{3}) a été observée chez 32,6 % des patients et 21,8 % des cycles. Aucune thrombocytopénie sévère (< 50 000/mm ^{3}) n'a été observée.

Un cas de thrombocytopénie périphérique avec anticorps antiplaquettes est rapporté dans l'expérience clinique obtenue après la mise sur le marché.

Infection :

De rares cas d'insuffisance rénale, d'hypotension ou de collapsus cardiovasculaire ont été observés chez des patients atteints d'infection systémique grave.

Effets indésirables généraux et réactions au site d'injection :

- Syndrome cholinergique aigu : Un syndrome de type cholinergique aigu, transitoire et sévère, est observé chez 9 % des patients traités par monothérapie et chez 1,4 % des patients traités par association. Les principaux symptômes sont définis par une diarrhée précoce et un ensemble de symptômes tels que crampes abdominales, conjonctivites, rhinites, hypotension, vasodilatation, hypersudation, refroidissement, malaises, vertiges, troubles visuels, myosis, larmoiements et hypersalivation survenant pendant ou dans les 24 heures suivant l'administration de Campto. Les symptômes cèdent à l'administration d'atropine (cf Mises en garde/Précautions d'emploi).L'asthénie sévère a été observée chez moins de 10 % des patients traités par monothérapie et chez 6,2 % des patients traités par association. L'imputabilité à Campto n'est pas clairement établie. Une fièvre isolée non accompagnée d'infection ou de neutropénie sévère est survenue chez 12 % des patients traités par monothérapie et chez 6,2 % des patients traités par association. Des réactions modérées au site d'injection ont été peu fréquemment rapportées.

- Troubles cardiovasculaires : de rares cas d'hypertension pendant ou suivant la perfusion ont été rapportés.

- Troubles respiratoires : de rares cas de pneumopathie interstitielle et de pneumonie avec infiltrats pulmonaires ont été observés. Des effets précoces tels que dyspnée ont été rapportés.

- Atteintes cutanées et sous-cutanées : l'alopécie est très fréquente et réversible. Des réactions cutanées d'intensité modérée et peu fréquentes ont été rapportées.

- Troubles du système immunitaire : des réactions allergiques d'intensité modérée et peu fréquentes et de rares cas de réactions de type anaphylactique/anaphylactoïde ont été rapportés.

- Troubles musculosquelettiques : des effets précoces tels que contraction musculaire ou crampes et paresthésies ont été rapportés.

Examens biologiques : En monothérapie, une augmentation transitoire mineure à modérée des taux sériques soit des transaminases, soit des phosphatases alcalines, soit de la bilirubine est observée respectivement chez 9,2 %, 8,1 % et 1,8 % des patients, en l'absence de progression des métastases hépatiques. Une augmentation transitoire mineure à modérée des taux sériques de créatinine est observée chez 7,3 % des patients. En association, une élévation sérique transitoire (grade 1 et 2) des ALAT, ASAT, phosphatases alcalines ou bilirubine a été observée chez 15 %, 11 %, 11 % et 10 % des patients respectivement, en l'absence de progression des métastases hépatiques. Des grades 3 transitoires ont été observés chez 0 %, 0 %, 0 % et 1 % des patients respectivement. Aucun grade 4 n'a été observé. Dans de très rares cas, une élévation de l'amylase sérique et/ou de la lipase sérique a été rapportée. De rares cas d'hypokaliémie principalement liée à une diarrhée et des vomissements ont été rapportés. *Troubles du système nerveux :* de très rares cas de troubles du langage transitoires ont été rapportés lors de perfusions de Campto.

Extrait du RCP 5 Fluorouracile-

DC/EFFETS INDÉSIRABLES

Stomatite, Inflammation muqueuse, Diarrhée, Anorexie, Nausée, Vomissement, Hémorragie digestive (Exceptionnel), Coloration de la peau, Alopécie, Dermatite, Eruption cutanée, Urticaire, Photosensibilisation, Douleur précordiale, Electrocardiogramme(anomalie), Infarctus du myocarde (Exceptionnel), Leucopénie, Thrombopénie, Anémie (Rare), Ataxie, Larmoiement

Extrait du RCP de l'acide folinique

DC/EFFETS INDÉSIRABLES

Ils sont fonction de la dose et du schéma d'administration du 5-fluorouracile :

diarrhée : chez le sujet âgé, risque de déshydratation (cf Mises en garde/Précautions d'emploi) ; mucite, stomatite (cf Mises en garde/Précautions d'emploi) ; réactions cutanées : sécheresse de la peau, érythème ; conjonctivite, larmoiement ; toxicité hématologique modérée.

Extrait du RCP gemcitabine – GEMZAR®

DC/EFFETS INDÉSIRABLES

- Hématologiques : La gemcitabine peut induire une aplasie médullaire, entraînant une anémie, une leucopénie et une thrombocytopénie. La myélosuppression est généralement modérée, elle est plus prononcée pour la lignée granulocytaire. La thrombocytémie est un autre effet fréquemment rapporté.

- Hépatiques : Des augmentations des transaminases hépatiques sont observées. Elles sont habituellement faibles, transitoires et ne nécessitent que rarement l'arrêt du traitement. La prudence s'impose toutefois chez les patients dont la fonction hépatique est altérée.

- Œso-gastro-intestinaux : Nausées, parfois accompagnées de vomissements. Ces effets secondaires justifient des mesures thérapeutiques dans approximativement 20 % des cas, mais n'imposent que rarement la diminution de la dose et sont faciles à traiter par les antiémétiques classiques. Diarrhées, toxicité buccale à type de mucite.

- Pulmonaires : Dans les heures qui suivent l'injection de gemcitabine, les patients peuvent présenter une dyspnée, qui est généralement d'intensité faible et de courte durée. Elle nécessite rarement une réduction de

la posologie et disparaît habituellement sans traitement spécifique. Son mécanisme est inconnu et sa relation avec la gemcitabine n'est pas claire. Des cas d'œdème pulmonaire, de pneumopathies interstitielles et de syndrome de détresse respiratoire de l'adulte (ARDS), d'étiologie inconnue, ont été rapportés au cours du traitement par gemcitabine. Dès leur survenue, l'arrêt de la gemcitabine doit être envisagé.

- Rénaux : Une protéinurie et une hématurie modérées surviennent chez près de la moitié des patients, mais sont rarement significatives sur le plan clinique ; elles ne sont habituellement pas associées à des modifications de la créatinine sérique ou de l'urémie. On a cependant rapporté quelques cas d'insuffisance rénale d'étiologie incertaine. Aucune toxicité rénale cumulative n'a été observée (cf Mises en garde/Précautions d'emploi).Des manifestations cliniques compatibles avec un syndrome hémolytique et urémique ont été rapportées chez les patients recevant de la gemcitabine. Le traitement par gemcitabine doit être interrompu dès les premiers signes d'anémie hémolytique micro-angiopathique tels qu'une chute brutale de l'hémoglobine avec thrombocytopénie concomitante, élévation de la bilirubine sérique, de la créatinine sérique, de l'urée sanguine ou de la LDH. L'insuffisance rénale peut ne pas être réversible, même à l'arrêt du traitement, et une dialyse peut être nécessaire.

- Allergiques : Des éruptions peuvent survenir et s'accompagner de prurit. L'éruption est habituellement faible, ne nécessite pas de réduction posologique et répond à un traitement local. Une desquamation, une vésiculation et une ulcération sont des effets secondaires rapportés occasionnellement. Un bronchospasme a parfois été rapporté. Ce bronchospasme est habituellement d'intensité modérée et passager, mais il peut requérir un traitement parentéral. La gemcitabine ne doit pas être administrée aux patients ayant une hypersensibilité connue à ce produit. De rares cas de réaction anaphylactique ont été rapportés.

- Cardiaques : Des cas d'infarctus du myocarde, d'insuffisance cardiaque congestive et d'arythmie ont été observés. On a rapporté quelques cas d'hypotension.

- Cutanés : Des manifestations cutanéomusculaires sévères à type de dermatopolymyosite, au niveau du site antérieurement irradié, ont été rapportées après administration successive de radiothérapie et de gemcitabine.

- Autres : Un syndrome grippal rarement sévère peut survenir. Il est généralement de courte durée et nécessite rarement une diminution de la posologie. Fièvre, céphalées, dorsalgie, frissons, myalgies, asthénie et anorexie sont les symptômes les plus communément rapportés. De même, une toux, une rhinite, des malaises, des sueurs et une insomnie sont couramment signalés. La fièvre et l'asthénie sont également rapportées comme symptômes isolés. Le mécanisme à la base de cette toxicité est inconnu. Le paracétamol peut en atténuer les symptômes.
Œdème périphérique, très rarement œdème facial. L'œdème périphérique est habituellement modéré et n'impose que rarement une réduction de la posologie, mais peut être douloureux ; il est généralement réversible après l'arrêt de la gemcitabine. Le mécanisme à la base de cette toxicité est inconnu. Il n'y a aucune association avec des signes d'insuffisance cardiaque, hépatique ou rénale. Les effets secondaires suivants sont aussi couramment rapportés : alopécie (en général minime), somnolence.

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Unité de Biostatistique
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Plan d'Analyse Statistique (Phase III)

PROTOCOLE ACCORD 11/0402

N° EudraCT : 2004-001985-42

ETUDE RANDOMISEE DE PHASE II/III COMPARANT L'ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] A LA GEMCITABINE EN PREMIERE LIGNE DE CHIMIOTHERAPIE DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Version 1, 03/07/2009

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ACCORD 11/0402	
TITRE	ETUDE RANDOMISEE DE PHASE II/III COMPARANT L'ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] A LA GEMCITABINE EN PREMIERE LIGNE DE CHIMIOTHERAPIE DE PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE
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Version	1
Date	10 juillet 2009

Page de SIGNATURES

J'ai lu ce plan d'analyse statistique et confirme que tous les objectifs d'étude comme indiqués dans le protocole sont couverts.
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TABLE DES MATIERES

LISTE DES ABBREVIATIONS ET DEFINITION DES TERMES

Abbréviations	Définition
EI	Evénements intercurrents (AE=adverse event)
ALAT	Alanine amino transferase
PAL	Phosphatase Alkaline
ASAT	Aspartate amino transferase
BSA / SC	Body Surface Area / Surface corporelle
SC / BSA	Surface corporelle / Body Surface Area
CRF	Case Report Form
DI	Dose Intensity / Dose intensité
DMC	Data Monitoring Committee
ECG	Electrocardiogramme
EORTC	European Organisation for Research and Treatment of Cancer
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
ITT	Intention–to-treat / Intention de Traiter
NCI-CTC	National Cancer Institute - Common Toxicity Criteria
QLQ-C30	Quality of Life Questionnaire – C30
QLQ-PAN24	Quality of Life Questionnaire – PAN24
RDI	Relative Dose Intensity / Dose intensité relative
PAS	Plan d'Analyse Statistique

1 RATIONEL

Le plan d'analyses statistiques (PAS) décrit les analyses statistiques à réaliser pour l'étude ACCORD 11/0402-Prodige 4 concernant la partie phase III.
Un bref descriptif de la planification de l'étude sera réalisé, suivi par le détail des populations d'analyse et des méthodes statistiques utilisés. Les tables et listings à produire seront détaillés
Ce PAS a été rédigé à partir des documents suivants :

- Protocole original contenant l'ensemble des amendements (version 9).
- International Conference on Harmonisation (ICH) guideline E9 (Statistical Principles for Clinical Trials).

2 OBJECTIFS DE L'ETUDE

L'objectif principal de l'étude est d'évaluer l'efficacité en terme de survie globale de l'association oxaliplatine, irinotecan, 5 fluorouracile et acide folinique (Folfirinox – bras A) dans le traitement du cancer du pancréas métastatique par rapport au traitement de référence par gemcitabine (bras B).

Phase III:

Objectif principal:

- Comparer la survie globale globale entre les deux schémas thérapeutiques, l'association Folfirinox – bras A par rapport au traitement de référence par gemcitabine bras B.

Objectifs secondaires:

- Comparer la survie sans progression entre les 2 bras
- Comparer la qualité de vie entre les 2 bras.
- Comparer les taux de réponse
- Comparer la toxicité aux traitements
- Evaluer la qualité de vie selon les questionnaires EORTC QLQ-C30 et PAN 24.

3 METHODOLOGIE DE L'ETUDE

3.1 Description

Cet essai est une phase II/III, multicentrique, randomisé.
Quatre vingt huit patients ayant un cancer du pancréas métastatique seront randomisés dans l'étude de phase II. A la fin de la phase II, si la décision de continuer en phase III est prise, 272 patients supplémentaires seront randomisés en phase III pour atteindre un total de 360 patients

Les patients seront randomisés 1 :1 selon les deux bras de traitements suivants :

- **Bras A : Folfirinox** (oxaliplatine (Eloxatine®) 85 mg/m2 J1 en 2h, puis irinotecan (Campto®)180 mg/m2 J1 en 90mn + acide folinique 400 mg/m2, J1 en 2h (pendant la perfusion d'irinotécan) + 5-FU bolus 400 mg/m² J1 suivi de 5-FU continu 2,4 g/m2 au total sur 46 heures, soit 1,2 g/m2 à J1 et 1,2 g/m2 à J2).

- **Bras B : gemcitabine** (1000 mg/m2 en 30 mn par voie intra veineuse stricte, à J1, J8, J15, J22, J29, J36, J43 ; Reprise de la gemcitabine à J57, 3 semaines sur 4 (J57, J64, J71 suivi d'une semaine de pause)).

3.2 Plan de l'étude

3.2.1 Durée de l'étude

Les patients inclus dans le bras A (Folfirinox) seront traités jusqu'à la progression et un maximum de 12 cycles est conseillé.

Les patients inclus dans le bras B (gemcitabine) seront traités jusqu'à la progression et un maximum de 6 mois est conseillé.

Au delà de cette période de traitement protocolaire, la prise en charge médicamenteuse ou non du patient, est laissé au libre choix de l'investigateur.

De même en cas de progression, la prise en charge thérapeutique du patient est laissé au choix de l'investigateur.

L'ensemble des patients seront suivis jusqu'au décès.

3.2.2 Traitement

- **Bras A : Folfirinox**
  - oxaliplatine (Eloxatine®)85 mg/m2 J1 en 2h,
  - irinotecan (Campto®)180 mg/m^2 J1 en 90mn,
  - acide folinique 400 mg/m2, J1 en 2h (pendant la perfusion d'irinotécan),
  - 5-FU bolus 400 mg/m^2 J1 suivi de 5-FU continu 2,4 g/m2 au total sur 46 heures, soit 1,2 g/m2 à J1 et 1,2 g/m2 à J2).

- **Bras B : gemcitabine**
  - gemcitabine (1000 mg/m2 en 30 mn par voie intra veineuse stricte, à J1, J8, J15, J22, J29, J36, J43 ; Reprise de la gemcitabine à J57, 3 semaines sur 4 (J57, J64, J71 suivi d'une semaine de pause)).

3.2.3 Méthode d'allocation des traitements

Une randomisation centralisée (Sous Oracle Forms par Euraxi pharma) a été réalisée selon la méthode de minimisation selon les facteurs de stratification suivants :

- l'état général OMS (0 vs 1),
- la localisation (tête vs autre).
- le centre (n modalités),

Les patients seront randomisés selon selon un ratio 1:1 dans les deux bras de traitement :
Bras A: Folfirinox
Bras B: gemcitabine.

3.3 Comité de surveillance - Data Monitoring Committee (DMC)

Un DMC indépendant (iDMC) a été constitué afin de suivre l'évolution des inclusions dans l'étude, la tolérance et l'efficacité des traitements administrés. L'iDMC, est constitué de 2 oncologues médicaux, 2 radiothérapeutes et un statisticien ne participant pas à l'étude.

L'iDMC sera sollicité pour chacune des étapes des analyses intermédiaires planifiées.

3.4 Décision de la Phase III

A la fin de la phase II, il a été décide de continuer les inclusions en phase III randomisée dont l'objectif principal est d'évaluer la survie globale.

3.5 Analyse intermédiaire au cours de la Phase III

Une analyse intermédiaire d'efficacité sera réalisée lorsque 2/3 des événements (décès) auront été observés soit **167 événements**.
Afin de maintenir un risque global de 5%, cette analyse intermédiaire ne sera considérée comme significative que si la p-value est inférieure ou égale à 0,001 et **p≤0,049** à l'analyse finale.

Le Comité de Surveillance (iDMC) pourra proposer l'arrêt prématuré de l'essai s'il le juge nécessaire et si l'ensemble des données disponibles provenant de l'essai ou d'autres sources est suffisamment convaincant pour influencer les pratiques thérapeutiques de la majorité des médecins.

4 DETERMINATION DU NOMBRE DE SUJETS NECESSAIRES

4.1 Phase II

Un total de 88 patients devait être inclus dans la phase II (44 par bras). En réalité, 97 patients ont été inclus et seront utilisés dans l'analyse de phase III.

4.2 Phase III

Pour mettre en évidence une différence dans les médianes de survie de 3 mois (passage de 7 à 10 mois de médiane), soit un risque relatif de 0.70, il faudra inclure **360 patients** pour maintenir un risque global alpha de 5 %, en acceptant un risque beta de 20 % (puissance de l'essai = 80%).
Cette puissance sera obtenue lorsque **250 événements** auront été observés (calcul effectué avec le logiciel East 5).

Etant donné que 97 patients ont été inclus au cours de la phase II, 263 patients restent à être inclus au cours de la phase III pour atteindre les 360 patients nécessaires.

5 EFFICACITE ET PARAMATRES DE TOLERANCE

5.1 Critère principal

Le critère principal est la **survie globale** étant calculée depuis la date de randomisation et la survenue du décès. Les patients vivants aux dernières nouvelles seront censurés.

5.2 Critères secondaires

Les critères secondaires sont les suivants :

- **Survie sans progression** étant le délai entre la date de randomisation à la date de première mise en évidence d'une progression documentée, la date du décès, ou la date des dernières nouvelles. Les patients vivants sans rechute seront censurés.
- **Taux de réponse** (selon les critères RECIST) : sera prise en compte la meilleure réponse enregistrée entre le début du traitement et la progression de la maladie ou la dernière évaluation (meilleure réponse globale optimale). La réponse est définie selon les critères RECIST. Toutes les réponses objectives doivent être confirmées 4 semaines après leur observation par un nouvel examen. Un comité indépendant de 2 radiologues experts relira toutes les évaluations tumorales radiologiques pour confirmer les réponses enregistrées.
- **Durée de la réponse globale** étant calculée depuis la date à laquelle les critères de mesure définissant une réponse partielle ou complète sont rapportés jusqu'à la date de la documentation objective de la première progression,
- **Incidence de la toxicité** (selon l'échelle de toxicité NCI version 3.0),
- **Evaluation de la qualité de vie** selon le questionnaire EORTC QLQ-C30 (version 3) et le module spécifique EORTC-PAN24.

5.3 Paramètres de tolérance

Les paramètres de tolérance évalués seront l'ensemble des informations recueillies dans le cahier d'observation selon l'échelle CTC-NCI v3.0 après réconciliation avec les données de pharmacovigilance du promoteur.

6 DEFINITION DES POPULATIONS

Population ITT : l'ensemble des patients randomisés dans le bras de traitement (intention de traiter).

Population évaluable pour la tolérance : l'ensemble des patients randomisés ayant reçu au moins une cure ou une injection de traitement.

Population éligible : l'ensemble des patients randomisés ayant reçu au moins une dose de traitement et sans violation des critères d'inclusion ou de non inclusion.

Population évaluable pour la réponse tumorale :
À définir cf. PAS phase II

Une analyse en ITT sera réalisée sur l'ensemble des critères de jugement.

7 ANALYSES STATISTIQUES

7.1 Méthodes statistiques

7.1.1 Statistiques descriptives

Les variables quantitatives seront décrites par le nombre d'observations, la médiane, le minimum, et le maximum. Sauf indication contraire, la médiane sera présentée avec une décimale en plus de la valeur mesurée.
Les variables qualitatives seront décrites par le nombre d'observations (N) et la fréquence (%) avec le pourcentage par rapport à la population totale. Les catégories manquantes seront rajoutées pour rapporter l'ensemble des données. Les pourcentages seront présentés avec une décimale.
Les analyses descriptives seront résumées par bras de traitement et globalement seulement pour les caractéristiques initiales.

La "p-value" sera présentée avec 3 décimales sauf indication contraire.
Les tables et listings seront générées par STATA v10.0.

7.1.2 Variables qualitatives

Le test du Chi-2 sera utilisé pour comparer les proportions (ou test exact de Fisher si les fréquences attendues <5).
Les intervalles de confiance à 95% pour les proportions seront calculés par la méthode exacte Binomiale.

7.1.3 Données de Survie

Les données de survie correspondent à l'observation du délai pour qu'un événement particulier se produise (par exemple le temps jusqu'au décès).

La méthode de Kaplan-Meier sera utilisée pour analyser les données de survie et pour estimer les temps médian de survie. Les courbes de survie de Kaplan-Meier seront présentées. L'intervalle de confiance à 95% pour a médiane de survie sera calculé selon la méthode de Brookmeyer and Crowley (1982).
Les distributions de survie seront comparées par le test du logrank.

Les HRs et leurs IC95% seront estimés par un modèle à hazard proportionnel de Cox ajusté sur les facteurs de stratification utilisés pour la randomisation (OMS, localisation, centre). Le modèle de Cox sera utilisé pour comparer les distributions de survie après ajustement des éventuels facteurs pronostiques.

La validité des risques proportionnels sera évaluée graphiquement et/ou testée pour les covariables dépendantes du temps. Si une non proportionnalité des risques existe, les distributions de survie seront comparées par le test modifié de Kolmogorov-Smirnov,et ceci sera considéré comme support pour les comparaisons prévues par le test du logrank.

7.2 Définitions and conventions

7.2.1 Definitions

Age sera calculé ainsi :
Age = int((date at screening visit – date of birth) / 365.25)

Surface corporelle sera calculée selon la formule de Dubois and Dubois [2]
BSA/SC = (weight in kg) $^{0.425}$ * (height in m) $^{0.725}$ * 0.20247

Indice de Masse Corporelle sera calculé ainsi :
IMC= weight/ (height in m)²
Puis **IMC_cl** selon 4 catégories : maigres <18,5 / normaux<25 / surpoids<30 / obèses≥30

Jour 1 du cycle :
Le J1 du cycle est défini comme la date de 1ère administration du cycle.

Arrêt du traitement :
Les patients sont considérés sous traitement pour la durée du traitement et pour les 30 jours suivants l'arrêt du traitement.
L'arrêt du traitement est défini comme le dernier jour où le sujet reçoit un traitement à l'étude.

7.2.2 Conventions

Les délais jusqu'aux événements seront calculés à partir de la date de randomisation.
Pour tout calcul de délai ou de durée entre deux dates, la convention suivante sera appliquée : **[later date] – [earlier date] + 1 jour**.
Pour convertir un nombre de jours en année ou en mois, la convention suivante sera appliquée : **1 an = 365.25 jours**; **1 mois = 30.4375 jours**.

7.2.3 Données manquantes

Sauf indication contraire, les valeurs manquantes ne seront pas estimées.

7.2.4 Dates manquantes ou incomplètes

De la part d'EURAXI, convention lors de la 1ère analyse pour l'iDMC de décembre 2008 :
Si le jour d'une date est manquant, alors le jour central du mois (15) est attribué.

7.3 Caractéristiques des patients

Sur la population ITT

7.3.1 Disposition des patients

Les éléments suivants seront résumés par bras de traitement:

- Disposition des patients: population ITT (sujets randomisés), population évaluable pour la tolérance, population éligible, population évaluable pour la réponse tumorale.
- Administration des traitements et raison d'arrêt

Les listings suivants seront établis comme support :

- Sujets exclus de la population évaluable pour la tolérance (Sujet non traité)

- Sujets non éligibles
- Sujets non évaluables pour la réponse tumorale

7.3.2 Déviations au protocole

Suite à l'iDMC de décembre 2008, la notion de déviation majeure ou mineure est inutile étant donné que l'ensemble des analyses seront réalisée en ITT.

7.3.3 Facteurs de la randomisation

Les facteurs relevés au moment de la randomisation seront décrits :

- Sexe: homme/femme : fréquence et %
- Age (années) : médiane et étendue
- Etat général OMS : fréquence et %
- Localisation tumorale : fréquence et %

7.3.4 Caractéristiques démographiques

Les caractéristiques démographiques seront résumées selon les informations de la randomisation et du bilan d'inclusion.

- Sexe: homme/femme : fréquence et %
- Age (années) : médiane et étendue
- Etat général OMS : fréquence et %
- Poids (kg) : médiane et étendue
- Taille (cm) : médiane et étendue
- Surface corporelle (m^2) : médiane et étendue
- IMC (kg/m^2) sera calculé : médiane et étendue

Les groupes seront comparés pour évaluer la comparabilité initiale sur ces caractéristiques.

7.3.5 Examens physiques et QLQ-C30

Les examens réalisés à l'inclusion seront décrits :

- Scanner thoraco-abdominopelvien: délai par rapport à la randomisation, fréquence et % du résultat normal/anormal,
- ECG : délai par rapport à la randomisation, fréquence et % du résultat normal/anormal,
- Test de grossesse chez les femmes : délai par rapport à la randomisation, fréquence et % du résultat positif/négatif.
- Qualité de vie QLQ-C30 : score initiaux des 8 dimensions évaluées / médiane et étendue

7.3.6 Caractéristiques de la maladie

Les groupes seront comparés pour évaluer la comparabilité initiale sur ces caractéristiques.

7.3.6.1 Tumeur primitive

Les caractéristiques de la tumeur primitive seront résumées selon les informations du bilan d'inclusion (CRF p3).

- Délai du diagnostic à partir de la randomisation
- Type de diagnostic, différenciation
- Délai Randomisation/évaluation tumorale

- Type d'examen, classification pTNM, cTNM
- Localisation de la tumeur primitive
- Dimension maximale de la tumeur
- Traitements antérieurs éventuels (naute, délais par rapport à la randomisation)

7.3.6.2 Tumeur métastatique

Les caractéristiques de la tumeur métastatique seront résumées selon les informations du bilan d'inclusion (CRF p3).

- Délai du diagnostic à partir de la randomisation
- Type de diagnostic, différenciation
- Délai Randomisation/évaluation tumorale
- Type d'examen, classification pTNM, cTNM
- Traitements antérieurs éventuels (naute, délais par rapport à la randomisation)
- Marqueurs tumoraux (CA19-9, ACE)
- Nombre de sites métastatiques
- Nature des sites métastatiques
- Nombre de lésions mesurables et non mesurables et sites

7.3.7 Biologie initiale et marqueurs tumoraux

Les résultats biologiques initiaux suivants ont été identifies comme « Non fait »/ « normaux »/ « anormaux » et seront décrit tels quels :

- Bilan hématologique: Hémoglobine, neutrophiles/granulocytes, plaquettes, TP et autres hématologie.
- Bilan biochimique: Calcium, Glycémie, albumine, protidémie, autre
- Bilan hépatique : bilirubine totale/libre, LDH, Phosphatase alkaline (PAL), ALAT (SGPT), ASAT (SGOT), Gamma GT, autre
- Bilan rénal : Créatininémie, autre.

7.4 Traitements étudiés

7.4.1 Bras A : FOLFIRINOX

Seront décrit pour chaque drogue :

- Le nombre de cycles administrés,
- La dose cumulée (mg/m²)
- La dose intensité (mg/m²/semaine)
- La dose intensité relative
- Modification : Nombre de réductions, d'arrêts et raisons
- Retards des administrations et raisons

7.4.2 Bras B : Gemcitabine

Seront décrit :

- Le nombre de cycles administrés, de perfusion
- La dose cumulée (mg/m²)
- La dose intensité (mg/m²/semaine)
- La dose intensité relative
- Modification : Nombre de réductions, d'arrêts et raisons
- Retards des administrations et raisons

7.5 Efficacité

7.5.1 Survie globale (critère principal)

Population: ITT

Globalement et par bras de traitement, seront données :

- Le suivi médian,
- La survie globale médiane,
- Les taux de survie globale à 6 et 12 mois,
- Le nombre d'événements observés,
- Le nombre de sujets à risque
- Le test du logrank associé
- Le modèle de Cox stratifié sur les facteurs de stratification (HR et IC95%) univarié et multivarié,
- Les courbes de survie globale.

7.5.2 Survie sans progression

Population: ITT

Globalement et par bras de traitement, seront données :

- La survie sans progression médiane,
- Les taux de survie sans progression,
- La nature et le nombre d'événements observés,
- Le nombre de sujets à risque
- Le test du logrank associé
- Le modèle de Cox stratifié sur les facteurs de stratification (HR et IC95%) univarié et multivarié,
- Les courbes de survie sans progression.

7.5.3 Taux de réponse objective et durée de la réponse

Population: ITT, Population évaluable pour la réponse

La réponse tumorale a été évaluée selon les critères RECIST.

Le taux de réponse globale de la 1ère évaluation sera décrit par bras de traitement par la fréquence de chaque type de réponse, le % et les intervalles de confiance à 95%.

Le meilleur taux de réponse globale sur l'ensemble des évaluations sera décrit par la fréquence de chaque type de réponse et son % et l'intervalle de confiance à 95% associé pour chaque bras de traitement.
Le test de chi-2 ou de Fisher's Exact si approprié seront utilisés pour comparer les bras de traitement en terme de taux de réponse.

La durée de la réponse médiane sera estimée par la méthode de Kaplan-Meier.

7.6 Tolérance

7.6.1 Exposition au traitement

L'exposition aux traitements sera évaluée par la description des doses cumulées, dose intensité et dose intensité relative de chacune des drogue par patient et par bras de traitement.

La dose cumulée (mg/m²) :
La dose cumulée (mg/m²) par patient est la somme des doses totales administrées que le sujet à reçu au cours de l'étude rapporté à la surface corporelle (Somme doses (mg)/ SC(m²)).

7.6.1.1 5-FU

Les patients inclus dans le bras A FOLFIRINOX auront reçu un bolus de 400mg/m² plus une perfusion de 46 heures en continu de 2,4 g/m² pour chaque cycle (soit 1,2 g/m² à J1 et 1,2 g/m² à J2) après oxaliplatine, acide folinique et irinotecan.

La durée de traitement par 5-FU (en semaines) au cours de l'étude est définie comme : **[last dosing date – first dosing date + 13]/7**

La dose intensité et la dose intensité relative par patient seront calculées pour des cycles de 2 semaines.
La dose intensité (mg/m²/cycle) est définie comme :

$$\frac{\text{Dose cumulée de 5-FU (mg/m²)}}{\text{Durée de traitement par 5-FU (en semaines) / 2}}$$

La dose intensité relative est définie comme la dose intensité divisée par la dose prévue par cycle (2800 mg/m²/2 semaines=cycle).

7.6.1.2 Irinotecan (iri)

Les patients inclus dans le bras A FOLFIRINOX auront reçu une dose de 180 mg/m² IV en perfusion de 90 minutes après l'oxaliplatine.

La durée de traitement par l'irinotecan (en semaines) au cours de l'étude est définie comme : **[last dosing date – first dosing date + 14]/7**

La dose intensité et la dose intensité relative par patient seront calculées pour des cycles de 2 semaines.

La dose intensité (mg/m²/cycle) est définie comme :

$$\frac{\text{Dose cumulée de IRI (mg/m²)}}{\text{Durée de traitement par IRI (en semaines) / 2}}$$

La dose intensité relative est définie comme la dose intensité divisée par la dose prévue par cycle (180 mg/m²/2 semaines=cycle).

7.6.1.3 Oxaliplatin (oxa)

Les patients inclus dans le bras A FOLFIRINOX auront reçu une dose de 85 mg/m² IV en perfusion de 2 heures à J1 avant toute autre perfusion toutes les 2 semaines.

La durée de traitement par oxaliplatin (en semaines) au cours de l'étude est définie comme : **[last dosing date – first dosing date + 14]/7**

La dose intensité et la dose intensité relative par patient seront calculées pour des cycles de 2 semaines.

La dose intensité (mg/m²/cycle) est définie comme :

$$\frac{\text{Cumulative dose of Oxaliplatin (mg/m}^2\text{)}}{\text{Durée de traitement par oxaliplatin (en semaines) / 2}}$$

La dose intensité relative est définie comme la dose intensité divisée par la dose prévue par cycle (85 mg/m²/2 semaines=cycle) i.e.

$$\text{RDI} = \frac{\text{Dose Intensité}}{\text{Dose prévue}} = \frac{\dfrac{\text{Dose cumulée d'Oxaliplatin}}{\text{Durée de trt par oxaliplatin (sem)} \quad / 2}}{\text{Dose prévue (mg/m}^2\text{/cycle)}}$$

Ce qui peut être écrit comme :

$$\frac{\dfrac{\text{Dose cumulée d'Oxaliplatin}}{\text{[last dosing date – first dosing date + 14]/7}}}{\text{Planned dose} * \dfrac{\text{Nbre de cycles}}{\text{14*nbre de cycles /7}}}$$

7.6.1.4 Gemcitabine (gem)

Les patients inclus dans le bras B Gemcitabine auront reçu une dose de 1000 mg/m² en perfusion de 30 minutes apr IV stricte une fois par semaine pendant 7 semaines suivie de 14 jours de repos. Puis à partir du cycle suivant, l'administration est répétée une fois par semaine pendant 3 semaines consécutives, suivie d'une semaine de repos.

La durée de traitement par gemcitabine (en semaines) au cours de l'étude est définie comme : **[last dosing date – first dosing date + 7]/7**

La dose intensité et la dose intensité relative par patient seront calculées par semaine.

La dose intensité (mg/m²/semaine) est définie comme :

$$\frac{\text{Dose cumulée de gemcitabine (mg/m}^2\text{)}}{\text{Durée de traitement par gemcitabine (en semaines)}}$$

La dose intensité relative est définie comme la dose intensité divisée par la dose prévue par semaine (1000 mg/m²/semaines).

7.6.2 Evénements indésirables (EI)

Population évaluable pour la tolérance

Tous les événements indésirables liés aux traitements ont été recueillis seront décrits selon les groupes prédéfinis dans le CRF.
La gravité des EI sera grade selon l'échelle de toxicité du NCI-CTC (version 3.0).

Les EI seront décrits pour chaque bras de traitement par cycle et par patient.
Chaque EI sera décrit selon les 5 grades (0,1,2,3,4) et selon les grades 3/4.

Pour l'analyse par patient, si un EI est rapporté plus d'une fois au cours du traitement, le grade le plus sévère sera rapporté pour le patient.
Pour l'analyse par cycle, si un EI est rapporté plus d'une fois au cours d'un cycle de traitement, le grade le plus sévère du cycle sera rapporté pour le patient.

Le test de chi-2 ou de Fisher's Exact si approprié seront utilisés pour comparer les bras de traitement en terme d'incidence de toxicité de grade 3/4.

7.6.3 Données biologiques

Les données biologiques ont été recueillies au cours des cycles selon une cotation normale/anormale.
Elles seront décrites telles quelles pour chaque bras de traitement par cycle et par patient.
Pour l'analyse par patient, si une donnée biologique est rapportée anormale au moins une fois au cours du traitement, cette donnée sera rapporté pour le patient.
Pour l'analyse par cycle, si une donnée biologique est rapportée anormale au moins une fois au cours du cycle, cette donnée sera rapporté pour le patient.

7.6.4 Etat général OMS

L'évolution de l'état général OMS depuis le bilan d'inclusion jusqu'à la fin de l'étude sera présentée par bras de traitement.

7.6.5 Poids

Le poids étant mesuré à chaque cycle, l'évolution de ce paramètre depuis le bilan d'inclusion jusqu'à la valeur la plus basse après la 1ère dose de drogue sera codé selon l'échelle de toxicité CTC-NCI version 3.
L'incidence du pire changement de grade par patient sera décrit par bras de traitement. La perte et le gain de poids seront décrits.

Paramètre	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Gain/perte de poids	<5%	5 – <10%	10 – <20%	≥20%	--

7.6.6 Traitements concomitants

La prise de traitements concomitants et leur durée au cours des cycles seront décrites et listés par bras de traitement.

7.7 Qualité de Vie

La Qualité de vie sera évaluée par le questionnaire EORTC QLQ-C30 et le module spécifique validé EORTC PAN 24.

8 REFERENCES

[1] Haybittle JL: Repeated assessments of results in clinical trials of cancer treatment. Br J Radiol 1971;44:793-7

[2] DuBois D; DuBois EF: A formula to estimate the approximate surface area in height and weight be known. *Arch Int Med* 1916 17:863-71

Package leaflet: Information for the user

CAMPTO 20 mg/mL concentrate for solution for infusion
irinotecan hydrochloride, trihydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CAMPTO is and what it is used for
CAMPTO is an anticancer medicine containing the active substance irinotecan hydrochloride, trihydrate.
Irinotecan hydrochloride trihydrate interferes with the growth and spread of cancer cells in the body.
CAMPTO is indicated in combination with other medicines for the treatment of patients with advanced or metastatic cancer of the colon or rectum.

CAMPTO may be used alone in patients with metastatic cancer of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

2. What you need to know before you use CAMPTO
Do not use CAMPTO:
- if you have chronic inflammatory bowel disease and/or bowel obstruction
- if you are allergic to irinotecan hydrochloride trihydrate or any of the other ingredients of this medicine (listed in section 6 "What CAMPTO contains")
- if you are a breast-feeding woman (see section 2)
- if your bilirubin level is higher than 3 times the upper limit of the normal range
- if you have severe bone marrow failure
- if you are in poor general condition (WHO performance status higher than 2)
- if you are taking or have recently taken St John's Wort (a herbal extract containing Hypericum)
- if you are to take or have recently taken live attenuated vaccines (vaccines against yellow fever, chicken pox, shingles, measles, mumps, rubella, tuberculosis, rotavirus, influenza) and during the 6 months after stopping chemotherapy

If you receive CAMPTO in combination with other medicines, please make sure that you also read the package leaflet of the other medicines regarding additional contraindications.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using CAMPTO

Take special care with CAMPTO. The use of CAMPTO should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Diarrhoea
CAMPTO can cause diarrhoea, which in some cases may be severe. This may start a few hours or a couple of days after the medicine infusion. If left untreated, it could lead to dehydration and serious chemical imbalances, which can be life threatening. Your doctor will prescribe medicine to help prevent or control this side effect. Make sure you get the medicine right away, so that you will have it at home when you need it.

- Take the medicine as prescribed at the first sign of loose or frequent bowel movements.
- Drink large amounts of water and (or) salty drinks (fizzy water, soda or soup).
- Call your doctor or nurse know if you still have diarrhoea, especially if it lasts more than 24 hours, or if you get lightheaded, dizzy, or faint.

Neutropenia (decrease in some white blood cells)
This medicine can lower your white blood cell count, mainly in the weeks after the medicine is given. This can increase the risk of getting an infection. Be sure to let your doctor or nurse know right away if you have any signs of infection, such as fever (38 °C or higher), chills, pain when passing urine, a new cough, or bringing up sputum. Avoid being near people who are sick or have infections. Tell your doctor at once if you develop signs of infection.

Blood monitoring
Your doctor will likely test your blood before and during your treatment, to check for effects of the medicine on blood counts or on blood chemistry. Based on the test results, you may need medicines to help treat the effects. Your doctor may also need to reduce or delay your next dose of this medicine, or even stop it altogether. Keep all your appointments for doctor visits and lab tests.

This medicine may lower your platelet count in the weeks after it is given, which can increase your risk of bleeding. Speak with your doctor before taking any medicines or supplements that might affect your body's ability to stop bleeding, such as aspirin or aspirin-containing medicines, warfarin, or vitamin E. Tell your doctor right away if you have unusual bruising, or bleeding such as nosebleeds, bleeding gums when you brush your teeth, or black, tarry stools.

Nausea and vomiting
You may have nausea and vomiting on the day you receive this medicine or in the first few days after. Your doctor may give you medicine before your treatment to help prevent nausea and vomiting. Your doctor will likely prescribe anti-nausea medicines that you can take at home. Have these medicines on hand for when you need them. Call your doctor if you are unable to take fluids by mouth due to nausea and vomiting.

Acute cholinergic syndrome
This medicine may affect part of your nervous system that controls body secretions, leading to what is known as cholinergic syndrome. Symptoms can include runny nose, increased saliva, excess tears in the eyes, sweating, flushing, abdominal cramps, and diarrhoea. Let your doctor or

nurse know right away if you notice any of these symptoms, as there are medicines that can help control them.

Lung disorders
Rarely, people on this medicine have serious lung problems, Tell your doctor right away if you have new or worsening cough, trouble breathing, and fever. Your doctor may need to stop your treatment to manage this problem.

This medicine may increase your risk of major blood clots in the veins of the legs or lungs, which can travel to other parts of the body such as the lungs or brain. Tell your doctor right away if you notice chest pain, shortness of breath, or swelling, pain, redness, or warmth in an arm or leg.

Chronic intestinal inflammation and/or intestinal blockage
Call your doctor if you have pain in your belly and you cannot move your bowels, especially if you also have bloating and loss of appetite.

Irradiation therapy
If you recently received treatment with pelvic or abdominal radiotherapy, you may be at increased risk of developing bone marrow suppression. Please talk to your doctor before starting the CAMPTO.

Kidney function
Occurrences of kidney dysfunction have been reported.

Cardiac disorders
Inform your doctor if you suffer/suffered from heart disease or if you previously received anticancer medicines. Your doctor will monitor you closely and discuss with you how risk factors (for example smoking, high blood pressure and to high fat content) can be reduced.

Vascular disorders
CAMPTO is rarely associated with blood flow disorders (blood clots in the vessels of your legs and lungs) and it may occur rarely in patients with multiple risks factors.

Others
This medicine may cause sores in the mouth or on the lips, often within the first few weeks after starting treatment. This can cause mouth pain, bleeding, or even trouble eating. Your doctor or nurse can suggest ways to reduce this, such as changing the way you eat or how you brush your teeth. If needed, your doctor can prescribe medicine to help with the pain.

For contraception and breast-feeding information, refer to the information provided below under section Contraception, pregnancy, breast-feeding and fertility.

Tell your doctor or dentist that you are on this medicine if you are planning to have surgery or any procedure.

If used in combination with other anticancer medicines for your condition please make sure that you also read the leaflets for the other medicine.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Other medicines and CAMPTO
CAMPTO can interact with a number of medicines and supplements, which may either raise or lower the level of the medicine in your blood. Tell your doctor or pharmacist if you are using, have recently used or might use any of the following:

- Medicines used to treat seizure (carbamazepine, phenobarbital, phenytoin and fosphenytoin)
- Medicines used to treat fungal infection (ketoconazole, itraconazole, voriconazole and posaconazole)
- Medicines used to treat bacterial infection (clarithromycine, erythromycin and telithromycine)
- Medicines used to treat tuberculosis (rifampicin and rifabutin)
- St. John's Wort (a herbal dietary supplement)
- Live attenuated vaccines
- Medicines used to treat HIV (indinavir, ritonavir, amprenavir, fosamprenavir, nelfinavir, atazanavir, and others)
- Medicines used to suppress your body's immune system to prevent transplant rejection (cyclosporine and tacrolimus)
- Medicines used to treat cancer (regorafenib, crizotinib, idelalisib and apalutamide)
- Vitamin K antagonists (common blood thinner such as Warfarin)
- Medicines used to relax muscles used during general anaesthesia and surgery (suxamethonium)
- 5-fluorouracil/folinic acid
- Bevacizumab (a blood vessel growth inhibitor)
- Cetuximab (an EGF receptor inhibitor)

Tell your doctor, pharmacist or nurse before being given CAMPTO if you are already having, or have recently had chemotherapy (and radiotherapy).

Don't start or stop taking any medicines while you are on CAMPTO without talking with your doctor first.

This medicine can cause serious diarrhoea. Try to avoid laxatives and stool softeners while taking this medicine.

There may be more medicines that interact with CAMPTO. Check with your doctor, pharmacist or nurse about your other medicines, herbs, and supplements, and whether alcohol can cause problems with this medicine.

Contraception, pregnancy, breast-feeding and fertility
Contraception
If you are a woman of childbearing age, then you have to use effective contraception during and up to 6 months after stopping treatment.

As a man, you have to use effective contraception during and up to 3 months after stopping treatment. It is important to check with your doctor about what kinds of birth control can be used with this medicine.

Pregnancy
This medicine may cause problems with the foetus if taken at the time of conception or during pregnancy. Before initiating treatment, your doctor will ensure that you are not pregnant.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding
Irinotecan and its metabolite were measured in human milk. Breast-feeding should be discontinued for the duration of your treatment with this medicine.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking this medicine.

Fertility
No studies have been done, nevertheless, this medicine may affect fertility. Prior to taking this medicine talk with your doctor about the possible risk with this medicine and the options that may preserve your ability to have children.

Driving and using machines
You may notice that you are dizzy and/or have trouble with your vision in the first 24 hours or so after you take this medicine. Do not drive or operate machinery if you have this side effect.

CAMPTO contains sorbitol
This medicine contains a sugar (sorbitol). Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

This medicine contains 45 mg sorbitol in each mL which is equivalent to 90 mg/2 mL, 225 mg/5 mL and 675 mg/15 mL.

This medicine contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use CAMPTO
Always use this medicine exactly as your doctor has told you. Check with your doctor is you are not sure.
CAMPTO will be given to you by healthcare professionals.

Your doctor may recommend a DNA test before your first dose of CAMPTO.

Some people are genetically more likely to have certain side effects from the medicine.

The amount of CAMPTO that you will receive depends on many factors, including your height and weight, your general health or other health problems, and the type of cancer or condition being treated. Your doctor will determine your dose and schedule.

CAMPTO is injected into a vein through an intravenous route (IV). You will receive this injection in a clinic or hospital setting. CAMPTO must be given slowly, and the IV infusion can take up to 90 minutes to complete.

You may be given other medications to prevent nausea, vomiting, diarrhoea, and other side effects while you are receiving CAMPTO. You may need to keep using these medicines for at least a day after your CAMPTO injection.

Tell your care givers if you feel any burning, pain, or swelling around the IV needle when CAMPTO is injected. If the medicine escapes from the vein it can cause tissue damage. If you experience pain or notice redness or swelling at the IV site while you are receiving CAMPTO, alert your healthcare professional immediately.

There are currently several treatment schedules recommended for CAMPTO. It is usually given either once every 3 weeks (CAMPTO given alone) or once every 2 weeks (CAMPTO given in combination with 5FU/FA chemotherapy). The dose will depend on a number of factors, including the treatment schedule, your body size, your age and general health, your blood counts, how well your liver is working, whether you have had radiation to your abdomen/pelvis, and whether you have any side effects such as diarrhoea.

Only your doctor may assess the duration of treatment.

If you use more CAMPTO than you should
Seek emergency medical attention. Overdose symptoms may include some of the serious side effects listed in this medication guide.

If you forget to use CAMPTO
Call your doctor for instructions if you miss an appointment for your CAMPTO injection.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effect could be serious. You must immediately contact your doctor if you experience any of those following serious side effects (see section 2).

Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

- diarrhoea (see section 2)
- Early diarrhoea: Occurring within 24 hours of receiving this medicine, accompanied by symptoms runny nose, increased salivation, watery eyes, sweating, flushing, abdominal cramping. (This can occur while the medicine is being administered. If so, alert your healthcare professional promptly. Medication can be given to stop and/or lessen this early side effect).
- Late diarrhoea: Occurring greater than 24 hours of receiving this medicine. Because of concerns of dehydration and electrolyte imbalances with diarrhoea it is important to be

in contact with health care professionals for monitoring, and for medication and diet modifications advice.

Talk to your doctor or nurse if you experience any of the symptoms below:

Symptoms	**Frequency* of occurrence in Monotherapy**	**Frequency† of occurrence in Combination Therapy**
Abnormally low number of white blood cells which could put you at increased risk for infection	Very common	Very common
Low number of red blood cells causing tiredness and shortness of breath	Very common	Very common
Decreased appetite	Very common	Very common
Cholinergic syndrome (see Take special care with CAMPTO)	Very common	Very common
Vomiting	Very common	Very common
Nausea	Very common	Very common
Abdominal pain	Very common	Common
Hair loss (reversible)	Very common	Very common
Inflammation of mucous membranes	Very common	Very common
Fever	Very common	Common
Feeling weak and having no energy	Very common	Very common
Low number of platelets (blood cells that help with clotting) which may cause bruising or bleeding	Common	Very common
Abnormal liver function test values	Common	Very common
Infection	Common	Common
Low number of white blood cells with fever	Common	Common
Difficulty in passing stools	Common	Common
Abnormal kidney function test values	Common	Not reported

* Very common: may affect more than 1 in 10 people
† Common: may affect up to 1 in 10 people

Not known: frequency cannot be estimated from the available data

- Severe, persistent or bloody diarrhoea (which may be associated with stomach pain or fever) caused by bacteria called (*Clostridium difficile*)
- Blood infection
- Dehydration (due to diarrhoea and vomiting)
- Dizziness, rapid heart beat and pale skin (a condition called hypovolaemia)
- Allergic reaction

- Temporary speech disorders during or shortly after treatment
- Pins and needles
- High blood pressure (during or after infusion)
- Heart problems*
- Lung disease causing wheezing and shortness of breath (see section 2)
- Hiccups
- Intestinal blockage
- Enlarged colon
- Bleeding from the bowels
- Inflammation of the large intestine
- Abnormal lab test results
- Hole in the intestine
- Fatty liver disease
- Skin reactions
- Reactions at the site where the medicine was administered
- Low level of potassium in the blood
- Low level of salt in the blood mostly related with diarrhoea and vomiting
- Muscle cramps
- Kidney problems*
- Low blood pressure*
- Fungal infections
- Viral infections

* Infrequent cases of these events have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or infections of the blood.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CAMPTO
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month. Your doctor will check this for you.

Storage conditions
Store below 25 °C.
Store in the original outer carton, protect from light.

Shelf life
Before dilution: 2 years (40 mg in 2 mL presentation) or 3 years (100 mg in 5 mL and 300 mg in 15 mL presentations).

After dilution: The medicine will be given to you within 24 hours of dilution. The diluted solution may have been stored at 2 °C to 8 °C in a refrigerator.

6. Contents of the pack and other information

What CAMPTO contains

The active substance is
Irinotecan hydrochloride, trihydrate 20 mg/mL
equivalent to irinotecan 17.33 mg/mL

One vial of 2 mL contains 40 mg of irinotecan hydrochloride trihydrate (40 mg/2 mL).
One vial of 5 mL contains 100 mg of irinotecan hydrochloride trihydrate (100 mg/5 mL).
One vial of 15 mL contains 300 mg of irinotecan hydrochloride trihydrate (300 mg/15 mL).

The other ingredients are
Sorbitol E420 (see section 2), lactic acid, sodium hydroxide, hydrochloric acid and water for injections.

What CAMPTO looks like and contents of the pack

This medicine is supplied as concentrate for solution for infusion in amber-coloured polypropylene vials of 2 mL, 5 mL or 15 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

Manufacturer
Pfizer Service Company BVBA
Hoge Wei 10
1930, Zaventem
Belgium

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium	Campto 20 mg/mL, solution à diluer pour perfusion
France	Campto 20 mg/mL, solution à diluer pour perfusion (IV)
Greece	Campto 20 mg/mL, concentrate for solution for infusion
Ireland	Campto 20 mg/mL, concentrate for solution for infusion
Italy	Campto 20 mg/mL, concentrato per soluzione per infusione
Luxembourg	Campto 20 mg/mL, solution à diluer pour perfusion

Netherlands	Campto 20 mg/mL, concentraat voor oplossing voor infusie
United Kingdom	Campto 20 mg/mL, concentrate for solution for infusion

This leaflet was last revised in 05/2021

Ref: CF 21_0

The following information is intended for healthcare professionals only

Instruction for personnel regarding safe handling of CAMPTO

Like all anti-neoplastic substances, irinotecan must be prepared and handled carefully. The use of protective glasses, mask and gloves is required.

If CAMPTO comes into contact with your skin, wash it off immediately and thoroughly with soap and water. If CAMPTO comes into contact with your mucous membranes, wash it off immediately and thoroughly with water.

As with all injectable drugs, CAMPTO must be prepared under aseptic conditions.

If a clouding or condensation is visible in the vial or after dilution of the concentrate, the medicine may not be used and must be disposed of.

Preparation of the solution for infusion
As with any other injectable drugs, CAMPTO solution for infusion must be prepared aseptically.

If you observe any precipitate in the vial or solution for infusion, discard the product according to standard procedures for cytotoxic agents.

Aseptically withdraw the calculated amount of CAMPTO concentrate for solution for infusion from the vial into a syringe and transfer into a 250 mL infusion bag or bottle containing either 0.9% (w/v) sodium chloride solution or 5% (w/v) glucose infusion solution. Mix the solution for infusion in the infusion bag or bottle thoroughly by manual rotation.

Do not mix with other medicines.

Shelf life
The diluted CAMPTO solution is physically and chemically stable up to 28 days as a solution for infusion (9% (w/v) sodium chloride solution and 5% (w/v) glucose solution) when stored in LDPE or PVC containers at 5 °C or at 30 °C when protected from light.

When the diluted solution is not stored and protected from light, it is physically and chemically stable up to 3 days.

From a microbiological viewpoint, immediate use is recommended. If the product is not used immediately after dilution, the storage times and conditions are the responsibility of the user and

would normally not be longer than 24 hours at 2 °C to 8 °C, unless the dilution took place in controlled aseptic conditions.

Warnings against some visible signs of deterioration
Do not use CAMPTO if you notice a precipitate in the vials or the diluted solution. In this case, the product should be discarded according to the standard procedures for disposal of cytotoxic waste. Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Administration
For information on administration, please read the Summary of Product Characteristics for CAMPTO.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

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Your reference	Our reference	1 February 2022
EP 3 337 478	ESP00506SAN	MF/sh

Re.: European Patent No. 3 337 478
European Patent Application No. 16758337.6
Patentee: Ipsen Biopharm Ltd.
Opponent: Sandoz AG

In response to the reply of the patent proprietor to the notice of opposition dated 7th December 2021:

1. Cited documents

1.1 The following new prior art documents are referred to hereinafter:

D25: Tsai, C. *et al.*, *J. Gastrointest. Oncol.* **2011**, 185-194;

D26: Yoo, C. *et al.*, *Br. J. Cancer* **2009**, 101(10), 1658-1663;

D27: Kalra, A.V. *et al.*, *Cancer Res.* **2014**, 74(23), 7003-7013.

1.2 Documents D25 to D27 were published prior to the earliest priority date of the contested patent and are thus full prior art for all claims.

1.3 In reply to the notices of opposition, the patent proprietor filed an amended main request together with 35 densely-written pages of arguments. Claim 1 of the main request contains now the limitation that liposomal irinotecan is *"irinotecan sucrose octasulfate salt*

liposome injection". This new feature was not the subject matter of any of the dependent claims of the contested patent as granted.

1.4 The patentee then argued that secondary document D2 does not disclose that liposomal irinotecan MM-398 contains sucrose octasulfate (reply to the opposition, item 5.40). In this respect we had relied on review articles D5 and D7 as constituting evidence of the common general knowledge on MM-398 at the priority date of the contested patent. This was also contested by the patentee (reply to the opposition, items 5.71-5.74).

1.5 Moreover, the patentee filed with their reply a post-published article D18 and declaration D19 in support of their argument that the claimed dosage regimen has improved efficacy compared to the FOLFIRINOX dosage regimen of D3. They also argued that there is no hint in the prior art of the superior efficacy of liposomal irinotecan compared to conventional irinotecan (reply to the opposition, item 5.32).

1.6 As we will show below, review article D25 demonstrates that both the composition of MM-398 and its increased efficacy compared to conventional irinotecan belonged to the common general knowledge at the first priority date. Document D27 provides further evidence of said increased efficacy at much lower doses. These documents are thus a direct reaction to the amendment performed to the main request and to the inventive step arguments of the patentee.

1.7 As far as priority entitlement is concerned, the patentee chose to rely on paragraph [0075] of the first priority application as basis for the administration frequency of *"a total of once every two weeks"*. As we will show below, the claimed administration frequency is not directly and unambiguously derivable from the disclosure of the cited paragraph. In support of this argumentation, we will refer to document D26 as an example of the administration of irinotecan in two separated doses on day 1 and 3 that would be encompassed by the dosage regimen of the paragraph [0075] of the priority document, but not by claim 1 of the main request.

1.8 In conclusion, documents D25 to D27 are filed as a direct reaction to the reply to the opposition and are *prima facie* relevant for the assessment of the patentability of the claimed subject matter. They should thus be admitted to the proceedings.

2. Lack of priority

2.1 MM-398 liposomal irinotecan

2.1.1 As explained in the notice of opposition, claim 1 of the first priority application makes reference to *"MM-398 liposomal irinotecan"*, i.e., the ONIVYDE® formulation (contested patent, paragraph [0003]; prescribing information D4), while only *"liposomal irinotecan"* is mentioned in claim 1 as granted.

2.1.2 Claim 1 of the main request now contains the limitation that liposomal irinotecan is *"irinotecan sucrose octasulfate salt liposome injection"*. In other words, the formulation is an injectable formulation and contains sucrose octasulfate, an excipient used as entrapment agent. While the liposomal irinotecan of the main request is more specific than the one of claim 1 as granted, by no means it coincides with MM-398 / ONIVYDE® of the first priority document.

2.1.3 As indicated in the paragraph of D4 bridging pages 10 and 11, MM-398 contains 43 mg of irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar bilayer vesicle of approximately 110 nm in diameter, composed of specific amounts of DSPC, cholesterol and MPEG-2000-DSPE and containing HEPES and sodium chloride as further excipients. MM-398 is described also in prior art document D17. The choices of liposome type, composition, size, content of active ingredient, as well as the presence of further excipients are all critical to the stability of the liposomes and thus to their ability of delivering the active ingredient to the disease site. All these characteristics influence the dosage of liposomal irinotecan needed to achieved the desired therapeutic effect.

2.1.4 In conclusion, *"irinotecan sucrose octasulfate salt liposome injection"* and *"MM-398 liposomal irinotecan"* are not equivalent. The amendment made to the main request is immaterial for the assessment of the priority entitlement. The effective date of claim 1 is still the filing date.

2.2 The claimed doses

2.2.1 As already explained, a number of possible dosages for the various medicaments were mentioned in the first priority document, without any preference for the claimed dosages of 60 mg/m^2 of liposomal irinotecan and of 60 mg/m^2 of oxaliplatin.

2.2.2 The patentee tries to rely on claim 5 and 8 of the first priority document disclosing two dosages of 60 and 80 mg/m^2 for liposomal irinotecan and three dosages of 60, 75 and 85 mg/m^2 for oxaliplatin, respectively. The skilled person needed to select the dosage of 60 mg/m^2 of liposomal irinotecan from the first list and the dosage of 60 mg/m^2 for oxaliplatin from the second list. They needed to apply this combination of dosages to a specific pancreatic cancer (adenocarcinoma) at a specific stage (metastatic), without any pointer for the chosen combination.

2.2.3 The patentee relies as pointer to the claimed combination on *"dose level -1"* in table 7 of example 1 (paragraph [00288] on pages 59-60). However, the cited table makes clear in footnote *"d"* that said dose is for de-escalation only and that *"Enrollment in these dose levels will only be initiated upon agreement of the Investigators, the Sponsor, and the Medical Monitor"*. The skilled person thus understand that this is a less preferred dose combination. As already argued in paragraph 4.1.7 of the notice of opposition, the first priority document expressed a clear preference for a different dosage of liposomal irinotecan (80 mg/m^2). This is also apparent from the table cited by the patentee, whose footnote *"e"* specifies that *"Dose level 2 is the target dose for Arm I, based on Conroy et al. [1], and will be used in Part 2 of the study following dose confirmation according to methods described herein"*. Therefore, the priority application points to a dosage of 80 mg/m^2 of liposomal irinotecan and a dosage of 85 mg/m^2 for oxaliplatin as being preferred.

2.2.4 The preference for dosages of 60 mg/m^2 of liposomal irinotecan and 60 mg/m^2 of oxaliplatin became apparent only after obtaining the safety interim results of part 1 of the study of example 3. As the target doses were not well tolerated, they were slightly reduced. These interim results are disclosed in example 4 of the contested patent, which was however not present in any of the priority documents. The international application was amended accordingly, thus leading to a loss of priority.

2.2.5 In conclusion, no direct and unambiguous disclosure of the claimed dosage combination can be found in the first priority application. The same is true for each of the second to the sixth priority applications.

2.3 The administration frequency

2.3.1 No disclosure of the generic administration frequency of *"a total of once every two weeks"* can be found in the first priority document. While we agree with the patentee that literal support is not required, we have already shown in our notice of opposition that the dosage regimens disclosed in the first priority document are different from the claimed one.

2.3.2 The patentee believes that paragraph [0075] of the priority application discloses the claimed frequency of *"a total of once every two weeks"*:

> *"In various embodiments, the MM-398 liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil are administered to the patient with metastatic cancer not previously treated with a chemotherapeutic agent in the metastatic setting beginning on day 1 of a 2-week cycle wherein the method may include one or multiple cycles"*
> (first priority application, paragraph [0075])

2.3.3 While the quoted paragraph specifies that the administration of the 4 drugs must begin on day 1 of a 2-week cycle, it allows multiple administrations of, say, liposomal irinotecan. This is indeed a common way of administering irinotecan as it can be seen from document D26 in which the regimen mFOLFIRI (modified FOLFIRI) is used. Two doses of irinotecan are administered: the first on day 1 and the second on day 3, after the administration of 5-fluorouracil (D26, page 1659, left-hand column, second paragraph, or right-hand column, third paragraph).

2.3.4 On the other hand, claim 1 of the main request excludes a second administration of irinotecan, which must be administered instead *"a total of once every two weeks"* (emphasis added). It is thus clear that the claimed administration frequency cannot be derived from paragraph [0075] of the first priority application either. The same is true for each of the second to the sixth priority applications.

2.4 Claim 22 of the first priority document

The patentee argued on an auxiliary basis that claim 1 of the main request is directly and unambiguously derivable from claim 22 of the first priority application. This claim is directed to a very specific embodiment, which differs from claim 1 of the main request in no less than four ways, by own admission of the patentee (reply to the opposition, item 4.21).[1] There is no indication in the first priority application that this particular embodiment can be modified and combined *ad libitum* with features cherry-picked from different parts of the description. As this auxiliary position of the patentee is devoid of any merit, we refrain from providing further arguments at this stage.

3. Lack of inventive step

3.1. Introduction

3.1.1 In order to simplify the discussion, we will present two hypothetical scenarios in this submission:

1. the claims are only entitled to the filing date;[2]
2. the claims are entitled to the first priority date.

3.1.2 In the first scenario we will apply the problem solution approach starting from documents D1 or D6, both disclosing the protocol of the clinical trial of the patent. We refer instead to our notice of opposition for the alternative attack starting from D3.

3.1.3 In the second scenario, we will start from document D3 disclosing the mFOLFIRINOX (modified FOLFIRINOX) dosage regimen and rely only on documents published before the first priority date.

[1] We also note that a second dosage of oxaliplatin, most likely 85 mg/m^2, was meant to be specified after the word *"or"* in claim 22 of the first priority document, but was omitted by mistake.
[2] The scenario remains unchanged if claims are entitled to the 7th priority date, because there are no documents published between said date and the filing date.

3.2 The claims are only entitled to the filing date: D1/D6 as closest prior art

3.2.1 As explained in the notice of opposition, documents D1 and D6 disclose the protocol of the clinical trial of examples 3 and 4 of the contested patent. The trial is performed in patients with previously untreated metastatic pancreatic adenocarcinoma: D1 and D6 are thus directed to the same purpose of the contested patent. Experimental arm 1 involves the administration of nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin, the same four drugs of claim 1 and has thus the most technical features in common with claim 1. Experimental arm 1 of D1/D6 thus represents the closest prior art.[3]

3.2.2 The patentee argued that D1/D6 is not the closest prior art. On an auxiliary basis, they argued that experimental arm 2 of D1, with less features in common, is the closest prior art. These arguments are devoid of any merit.

3.2.3 It is evident to the skilled person that the clinical trial of D1 represents the most advanced development in the treatment of pancreatic cancer with an irinotecan containing regimen, because it makes use of the recently approved (see D4) liposomal formulation of irinotecan, which is known in the art for its improved safety and efficacy (see reviews D5, D7 and D25). This study represents therefore the most promising springboard for the alleged invention.

3.2.4 While it is true that the results of the study are not disclosed in D1 (nor in the contested patent), the Boards of Appeal have chosen several times the protocol of a clinical trial as the closest prior art (see, e.g., T 239/16). In the present case, D1 discloses the protocol of the very clinical trial on which the patentee relies for inventive step. Therefore, the choice of D1 as the closest prior art is fully in line with the practice at the European Patent Office.

3.2.5 The fact that the specific dosage regimen is not mentioned in D1 is of secondary importance, as the dosages of the 4 drugs in similar regimens belonged to the common general knowledge and thus mere routine adaptations of the known dosages to account for possible cumulative toxicities were necessary (see below in relation to obviousness). The administration frequency of once every two weeks was also the most commonly used when these drugs were used in combination (see below). These features are thus of secondary importance for the skilled person compared to the disclosure of the combination of the four specific drugs recited in claim 1.

[3] For brevity's sake, we will refer in the following to D1 only. The same arguments apply to D6 too.

3.2.6 Regarding the choice of the embodiment of D1 with less features in common with claim 1, as suggested by the patentee, this defies the established approach used at the EPO and thus deserves no further comments.

3.2.7 As the patentee was confronted with a closest prior art document very close to the claimed subject matter, they proposed a more distant starting point in the hope of being able to show the presence of an inventive step.

This is however bound to fail, because, in the event of revocation, it is sufficient to show on the basis of one relevant piece of prior art that the claimed subject-matter lacks an inventive step: there is no need to discuss which document is "closest" to the invention; the only relevant question is whether the document used is a feasible starting point for assessing inventive step.

As a consequence the proprietor cannot refute the argument that the claimed subject-matter lacks inventive step by submitting that a more promising springboard is available: a piece of prior art on the basis of which the claimed invention is considered non-obvious cannot be "closer" than a document on the basis of which the claimed invention appears obvious, because it is evident in this situation that the former does not represent the most promising springboard from which to arrive at the invention.

3.2.8 Arm 1 of D1 is directed to the same purpose and has the most (and the most relevant) technical features in common with the claimed subject matter. Its selection follows the approach commonly adopted by the Boards of Appeal. It is thus a feasible starting point for the assessment of inventive step. The problem solution approach should thus be applied (also) from D1.

3.3 The objective technical problem

3.3.1 D1 does not disclose the exact dosage regimen, nor the results of the clinical study. The effect of these differences is the confirmation of the efficacy and safety of the 4-drug combination proposed in D1 for the first-line treatment of metastatic adenocarcinoma of the pancreas.

3.3.2 The objective technical problem is therefore the provision of a safe and effective first-line treatment of metastatic adenocarcinoma of the pancreas. As already remarked, no specific degree of efficacy (e.g., compared to a different regimen or drug combination) is needed.

3.4 Obviousness

3.4.1 The solution to this problem is obvious based on the common general knowledge. This is in line with the established case law of the Boards of Appeal and, in particular, decisions T 2506/12, T 239/16, T 1760/08 and T 1409/06, which are fully applicable to the present case. We refer in this respect to section 5.3 of our notice of opposition.

3.4.2 To explain the routine selection of the optimal dosage regimen on the part of the skilled person, we have referred to review articles D3, D5 and D7. Review article D25 is filed herewith. All these documents are evidence of the common general knowledge at the relevant date, in line with the established case law (see T 777/08). We have thus discharged our burden of providing an account of the common general knowledge. The burden is now on the patentee to prove that the common general knowledge is not reflected in D3, D5, D7 and D25.

3.4.3 The patentee argues that the skilled person had several possible options from which to start to select the appropriate dosage regimen. However, the skilled person would have applied a dosage regimen similar to the one most commonly used when these four drugs are administered together.

3.4.4 The modified FOLFIRINOX (mFOLFIRINOX) regimen was the most commonly used at the relevant date for the treatment of pancreatic cancer, as evidenced by D3:

> *"Promising phase II results with FOLFIRINOX (FFX) [5] (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, bolus 5-fluorouracil 5FU) (400 mg/m^2, infusional 5FU 2400 mg/m^2 over 46 h, every 14 days) were confirmed in a sentinel phase III study (PRODIGE 4/ACCORD 11)"*
> (D3, paragraph bridging pages 853-854)

> *"With this scenario in mind, many modifications have been made (Table 2). Initially, physicians removed the bolus of 5FU, which is notably myelosuppressive, with some adding pegfilgrastim 6 mg on day 3 or 4. Commonly referred to as "mFOLFIRINOX," this seems to be the way it is often used today [18]."*
> (D3, pages 855, left-hand column, second paragraph, emphasis added)

3.4.5 Therefore, the claimed administration frequency of the four drugs once every two weeks and the claimed dosages of 5-fluorouracil and leucovorin were standard in the art. Nothing inventive can be seen in selecting a standard regimen belonging to the common general knowledge.

3.4.6 As far as liposomal irinotecan is concerned, it was commonly administered at a dosage of 80 mg/m^2 of the hydrochloride salt every two weeks when given in combination with 5-fluorouracil and leucovorin, as evidenced by review article D5:

> *"When given in combination with 5-fluorouracil/leucovorin, MM-398 is dosed at 70 mg/m^2 every 2 weeks (this is the free base equivalent to the 80 mg/m^2 dose of the salt form used in the NAPOLI-1 trial), with 5-fluorouracil dosed at 2400 mg/m^2 (as a continuous infusion over 46 h) and leucovorin at 400 mg/m^2, every 2 weeks."*
> (D5, executive summary, last bullet point)

3.4.7 Higher dosages of liposomal irinotecan of 120 mg/m^2 administered every 3 weeks, to which the patentee refers, where used only as monotherapy (D5, executive summary, second-last bullet point). They are thus clearly not relevant for a 4-drug dosage regimen.

3.4.8 Therefore, it remains to be established whether or not the skilled person would have slightly reduced the dosages of irinotecan and oxaliplatin to 60 mg/m^2 each to account for cumulative toxicities. This implies a mere reduction of 25% for liposomal irinotecan (from 80 to 60 mg/m^2) and of 30% for oxaliplatin (from 85 to 60 mg/m^2).

3.4.9 It belongs to the common general knowledge to reduce the dosages of anticancer drugs when given in combination (D9, page 1045, right-hand column, second paragraph; T 2506/12, r. 3.14 and r. 4.3). This is also highlighted in D3:

> *"As with usual practice, reduction in individual drug dosing is a standard approach for many of the common complications such as low blood counts, fever, infection, diarrhea, weight loss, and fatigue."*
> (D3, page 854, paragraph bridging the two columns, *"How is Toxicity of FFX Best Managed"*, emphasis added)

3.4.10 The patentee focuses their attention on the next sentence of D3 stating that not each and every toxicity problem can be solved by dose reduction and pointing to table 1 for other solutions to be used in patients with specific conditions, such as an allergy. This however does not detract anything from the fact that a dose reduction is the usual practice and the standard approach to deal with toxicities.

3.4.11 Indeed, review D3 teaches on page 855, left hand column, first and second paragraph, that *"many modifications have been made (Table 2)"* to the FOLFORINOX regimen to address the toxicity concerns of oncologists.

If we look at table 2, we see that oxaliplatin was administered in the study of Gunturu *et al.* and in the study of Metges *et al.* with a median dose intensity of 88% and 78%, respectively. This means that some patients received the standard dose, while others received a decreased dose, e.g., -20%, -30% or -40%, so that the median reductions were 12% and 22%, respectively. Instead, in the study of Alessandretti *et al.*, the dose of oxaliplatin was decreased to 50 mg/m^2 for all patients, which corresponds to a 40% reduction compared to the standard 85 mg/m^2.

As far as conventional (i.e., non-liposomal) irinotecan is concerned, whose standard dose in (m)FOLFIRINOX is 180 mg/m^2, we see in table 2 that Gunturu *et al.* and Metges *et al.* administered a median dose intensity of 64% and 81% (thus a median dose reduction of 36% and 19%), respectively, while Alessandretti *et al.* decreased the dose to 135 mg/m^2 for all patients, which corresponds to a 20% reduction compared to 180 mg/m^2.

3.4.12 In conclusion, it belonged to the common general knowledge to reduce the dosages of oxaliplatin and conventional irinotecan to account for the combined administration. The same necessarily applies to liposomal irinotecan as well. The claimed dose reductions of 25% for liposomal irinotecan (from 80 to 60 mg/m^2) and of 30% for oxaliplatin (from 85 to 60 mg/m^2) were fully within the ranged explored in the art and would have been selected by the skilled person based on routine investigations (the observation of dose limiting toxicities).

3.4.13 In conclusion, claim 1 of the contested patent does not involve an inventive step over any of documents D1 or D6 in the light of the common general knowledge and thus does not fulfil the requirements of Article 56 EPC.

3.5 The claims are entitled to the first priority date: D3 as closest prior art

3.5.1 For claims entitled to the first priority date, documents D1 and D6 are not available for the inventive step assessment. As explained in the notice of opposition, the mFOLFIRINOX dosage regimen disclosed in document D3 would be a suitable springboard for the alleged invention. Co-opponent 2 also proposed D3 or, alternatively, D10 or D11. All three documents relate to the FOLFIRINOX dosage regimen. While D3 discloses this regimen in more general terms, document D10 and D11 relate to a specific clinical trial (PRODIGE 4, NCT00112658).

3.5.2 The patentee argued that D10 is the most suitable closest prior art document for the claimed subject matter. As we will show below, they chose, again, a more distant and less promising starting point. On the other hand, the patentee decided to provide no defence starting from D3, thus implicitly accepting the lack of inventive step if the problem and solution approach is applied starting from D3.

3.5.3 Unlike D10, D3 discloses the modified FOLFIRINOX dosage regimen (mFOLFIRINOX), i.e., without the 5-fluorouracil bolus of 400 mg/m^2, and that it was the most commonly used at the relevant date (see paragraph 3.4.4 above). The mFOLFIRINOX regimen of D3 is closer to the claimed subject matter than the FOLFIRINOX regimen of D10 and thus represents a more promising springboard.

3.5.4 Moreover, D3 discloses that FOLFIRINOX is very frequently modified (D3, page 859, right-hand column, first paragraph; table 2), thus providing a pointer to another modification, the replacement of conventional irinotecan with liposomal irinotecan.

3.5.5 As a matter of fact, D3 was published in February 2015, only six months before the priority date of the contested patent. D10, instead, was published in May 2011, more than four years before the relevant date. Therefore, D3 correctly reflects the practice at the priority date of the contested patent, which had evolved in the years between the publication of D10 and that of D3.

3.5.6 In conclusion, D3 and the mFOLFIRINOX dosage regimen disclosed therein are a more promising starting point than D10. D3 represents therefore the closest prior art.

3.6 The objective technical problem

3.6.1 D3 does not disclose that liposomal irinotecan is administered to the patients. Standard irinotecan is administered instead. Moreover, oxaliplatin is administered at a dosage of 85 mg/m^2 instead of 60 mg/m^2 as in claim 1.

3.6.2 As no comparison is provided in the contested patent, the patentee relied on post-published document D18 and declaration D19 to argue improved efficacy. D10 discloses the results of the study of examples 3 and 4 of the patent. The claimed dosage regimen is named "NALIRIFOX" in D18.

3.6.3 First of all, the mFOLFIRINOX of D3 and not the FOLFIRINOX dosage regimen of D10 is the closest prior art.

3.6.4 Secondly, D18 makes crystal clear that the purpose of the study was not to compare the efficacy of NALIRIFOX with that of FOLFIRINOX or mFOLFIRINOX. Contrary to the wrong allegations of the patentee, the study aimed only at establishing the safety of the regimen:

> *"Primary objectives were to determine the maximum tolerated dose (MTD) and to evaluate safety and tolerability."*
> (D18, abstract, *"Methods"*; see also page 19, left-hand column, second paragraph)

3.6.5 As the skilled person knows well, it is not possible to directly compare the results of two different clinical studies, because of the differences in the patient populations and evaluation criteria. As the patentee admits (reply to the oppositions, page 13, footnote 22), different criteria were used in the study of D18 and in the study of D10. Moreover, D18 itself warns that no comparison with FOLFIRINOX or other regimens is possible:

> *"The safety of NALIRIFOX cannot be reliably compared with that of established therapies without head-to-head studies."*
> (D18, page 21, left-hand column, last paragraph, emphasis added)

> *"The efficacy of first-line NALIRIFOX warrants further investigation, given a median PFS of 9.2 months (95% CI: 7.69-11.96) and median OS of 12.6 months (8.74-18.69), although direct comparisons with other studies cannot be made. The outcomes of the PRODIGE 4 study are of interest, as these underpin the*

recommendations for the FOLFIRINOX regimen as first-line therapy in mPDAC [2,10,11,26]. FOLFIRINOX was associated with a median PFS of 6.4 months (95% CI: 5.5-7.2) and median OS of 11.1 months (9.0-13.1), using RECIST v1.0 [5]. However, important differences between the study populations include the proportions of patients with metastatic disease at study entry (recommended NALIRIFOX regimen: 90.6%; FOLFIRINOX in PRODIGE 4: 100%), the proportions with liver metastases (43.8% and 87.6%, respectively) and the median ages (58 and 61 years, respectively) [5].
(D18, page 21, right-hand column, third paragraph, emphasis added)

3.6.6 The patentee tried to address the different proportions of patients with metastatic disease with declaration D19. However, D18 explains that also the different proportions of patients with liver metastasis and the different median ages between the two studies are important differences. It goes without saying that these clear statements of the authors of D18 in a reputable peer-reviewed journal should be given substantially more weight than the interested declaration D19 of the vice president and global asset lead of the patentee.

3.6.7 In conclusion, the results of D18 cannot be compared with the closest prior art. The objective technical problem to be solved over D3 is the provision of an alternative first-line treatment of metastatic adenocarcinoma of the pancreas.

3.7 Obviousness

3.7.1 As explained in section 5.4 of our notice of opposition, the solution to this problem is obvious in the light of the common general knowledge, optionally in combination with D2 disclosing the preliminary results of the NAPOLI-1 trial. We note that the patentee did not provide any counterarguments on the obviousness the provision of an alternative dosage regimen (reply to the oppositions, item 5.81, which only contains a couple of standard sentences).

3.7.2 We note that even the scientists of the patentee confirm in D18 that the dosage regimen studied therein was based on FOLFIRINOX and the dosage regimen of the NAPOLI-1 trial, in other words, D3 in combination with D2:

"Dose exploration used a traditional 3 + 3 design (see Appendix); with dosing based on that administered in the NAPOLI-1 (liposomal irinotecan 70 mg/m²

free base equivalent) and PRODIGE 4 (FOLFIRINOX; oxaliplatin 85 mg/m²) pivotal studies [5,12]."
(D18, page 19, right-hand column, second paragraph, emphasis added)

3.7.3 The patentee argues that document D2 does not disclose the composition of liposomal irinotecan MM-398 and the fact that it contains sucrose octasulfate. However, the composition of MM-398 had been disclosed almost 10 years before the priority date in document D17 (see abstract and figure 1). Review article D25, which cites D17 as reference 27 and refers to MM-398 (also called PEP02) on pages 188 to 191 provides evidence that said composition belonged to the common general knowledge already 4 years before the priority date. Therefore, the skilled person knows that MM-398 contains *"irinotecan sucrose octasulfate salt liposome injection"* as recited in claim 1.

3.7.4 Even if the objective technical problem were to be formulated as the provision of a dosage regimen with improved efficacy, which we deny, its solution would have still been obvious for the skilled person. Indeed, it belonged to the common general knowledge that liposomal irinotecan MM-398 had improved safety and efficacy compared to conventional irinotecan (named CPT-11), as evidenced by review article D25:

"In a series of preclinical studies, nanoliposomal CPT-11 demonstrated significantly superior efficacy when compared to free CPT-11 at the same or higher dose, including frequent cures in some models. The superiority of nanoliposomal CPT-11 over free CPT-11 has been observed in different tumor models including colorectal, gastric, breast, cervical, glioma, pancreatic and lung cancer models. In addition to superior efficacy, nanoliposomal CPT-11 has shown a more favorable pharmacologic profile and reduced toxicity in multiple preclinical models."
(D25, page 189, left-hand column, second-last paragraph, emphasis added)

3.7.5 The studies mentioned in D25 are disclosed in detail in prior art document D27 dealing with the preclinical activity of nanoliposomal irinotecan (named Nal-IRI) and its active metabolite SN-38:

"For example, nal-IRI administered at doses 5-fold lower than free irinotecan achieved similar intratumoral exposure of SN-38 but with superior antitumor activity."

"Overall, our work shows how liposomal encapsulation of irinotecan can safely improve its antitumor activity in preclinical models by enhancing accumulation of its active metabolite within the tumor microenvironment."
(D27, abstract, emphasis added)

"The enhanced in vivo activity of nal-IRI as compared with free irinotecan was attributed to the ability of nal-IRI to extend the tumor SN-38 duration."
(D27, page 7012, left-hand column, second paragraph, emphasis added)

3.7.6 The skilled person would have thus replaced the conventional irinotecan of the mFOLFIRINOX dosage regimen of D3 with the improved liposomal formulation MM-398 with a reasonable expectation of obtaining even an improved first-line treatment of metastatic adenocarcinoma of the pancreas. Moreover, the skilled person would have adjusted the drug dosages without ingenuity, as explained in section 3.4 above.

3.7.7 Hence, claim 1 of the contested patent does not involve an inventive step over document D3 in the light of the common general knowledge or in combination with document D2 or document D27 and thus does not fulfil the requirements of article 56 EPC.

4. Auxiliary claim requests

4.1 In their reply to the notice of opposition, the patentee requested to maintain the contested patent according to the main request or any of auxiliary requests 1-3 filed therewith. In these requests, liposomal irinotecan is administered intravenously (AR1), the dependent claims are deleted (AR2), or both (AR3).

4.2. We agree with the patentee that the amendments of these auxiliary requests are immaterial for the assessment of inventive step, since it belonged to the common general knowledge that liposomal irinotecan, as well as the other drugs of the claimed dosage regimen, are administered by injection.

4.3 We however do not see how these auxiliary requests could help restoring priority entitlement. As the patentee provided no arguments in this respect, we cannot see how these requests are occasioned by a ground of opposition and thus comply with the requirements of Rule 80 EPC.

5. Conclusion

It has been shown above and in the notice of opposition that the contested patent is not in accordance with the requirements of Articles 56 EPC. Therefore, the request to revoke EP 3 337 478 in its entirety is fully justified.

Marco Fachini

Enc.
Documents D25-D27