UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC PHARMACEUTICAL GROUP LIMITED,
CSPC OUYI PHARMACEUTICAL CO., LTD., AND
CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioners,

v.

IPSEN BIOPHARM LTD,
Patent Owner.

Case No. IPR2025-00505
Patent No. 11,344,552

EXPERT DECLARATION OF MARK J. RATAIN, MD

Table of Contents

I, Mark J. Ratain, M.D., of Chicago, Illinois, declare as follows:

1. I have been retained by counsel for CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, "Petitioner"). I understand that Petitioner is submitting a petition for inter partes review ("IPR") of U.S. Patent No. 11,344,552 ("the '552 patent," attached as Ex.1001), which is assigned to Ipsen Biopharm Ltd. ("Patent Owner"). It is my understanding that Petitioner is requesting that the United States Patent and Trademark Office ("USPTO") cancel all claims of the '552 patent as unpatentable. I submit this expert declaration in support of Petitioner's IPR petition for the '552 patent. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

I. QUALIFICATIONS

2. I graduated from Harvard University magna cum laude in 1976 with an A.B. in Biochemical Sciences. I obtained my M.D. from Yale University School of Medicine in 1980. I completed my internship and residency in internal medicine at the Johns Hopkins Hospital in Baltimore, MD from 1980-1983. I completed a fellowship in Hematology and Medical Oncology at The University of Chicago Medical Center from 1983-1986.

3. I am board-certified in Internal Medicine, Medical Oncology, Hematology, and Clinical Pharmacology. I know of no other individuals in the United States with all these certifications.

4. In 1986, I joined the faculty of The University of Chicago as an Instructor and was promoted to Professor in 1995. In 2002, I was appointed to an endowed chair, the Leon O. Jacobson Professor in the Department of Medicine.

5. From 1992-2010, I served as Chairman of the University's interdepartmental unit in clinical pharmacology, most recently known as the Committee on Clinical Pharmacology and Pharmacogenomics. The Committee's main purpose is postdoctoral training in clinical pharmacology, primarily supported by a training grant from the National Institute of Health ("NIH"). In 2010, I founded a new Center for Personalized Therapeutics, and was also appointed the first Chief Hospital Pharmacologist at The University of Chicago Medical Center.

6. I have also had leadership roles in The University of Chicago's National Cancer Institute-designated Cancer Center since 1991, initially serving as Director of the Developmental Therapeutics Program. From 1999-2022, I served as the Associate Director for Clinical Sciences, with responsibility for strategic oversight of all oncology clinical trials at the Cancer Center. I continue to advise Cancer Centers around the country on research involving oncology drugs.

7. I also directed The University of Chicago Medicine's Developmental Therapeutics Clinic for more than 35 years, which focused on developing new treatment strategies for patients with a variety of malignancies, in particular patients with refractory gastrointestinal malignancies, including colorectal and pancreatic cancer.

8. I have extensive experience in the development of therapeutics, including small molecules, peptides, and proteins. This experience included membership on the Investigational Drug Steering Committee of the National Cancer Institute ("NCI") from 2005-2016, including leadership of that Committee from 2005-2008 and of its Clinical Trials Design Task Force from 2012-2016.

9. I have been directly involved in the design, conduct, and analysis of phase 1, 2, and 3 trials of more than 100 drugs, including small molecule, peptide, and protein drugs. Many of these clinical studies have included patients with pancreatic cancer, as detailed on my curriculum vitae, a copy of which is attached hereto as **Appendix A**. (Examples include but are not limited to Original Research Articles 3, 21, 36, 45, 49, 93, 111, 125, 129, 141, 160, 162, 163, 164, 169, 205, 231, 237, 261, 276, 291, 306, 307, 313, 317, 318, 334, 343, and 350.)

10. I have interacted extensively with the pharmaceutical industry as an investigator. In addition, I have consulted extensively for the pharmaceutical

industry for over 35 years, primarily regarding the development and commercialization of oncology drugs.

11. I have been extensively involved with the American Society of Clinical Oncology ("ASCO") since 1990, when I was appointed Chair of ASCO's Audit and Finance Committee. I was later elected Secretary-Treasurer of ASCO and served as an Officer and Director from 1994-1997. I also chaired a Subcommittee on Phase I Clinical Trials for ASCO's Public Issues Committee in 1996.

12. I have also been extensively involved with the American Society of Clinical Pharmacology and Therapeutics ("ASCPT"), an international organization comprised of clinical pharmacologists from academics, industry, and government (including FDA). Among other roles, I have served as a Director from 1997-2001, and chaired ASCPT's Program Committee for its 2003 meeting.

13. I have received numerous honors and awards, including from major societies in both oncology and clinical pharmacology. I received the 2011 Translational Research Professorship from ASCO for my work in the pharmacogenomics of anticancer agents, primarily for my work with irinotecan (sometimes referred to as CPT-11 or Camptosar). I have also been recognized for my work in clinical pharmacology by the Pharmaceutical Research and Manufacturer's Association of America Foundation (2015 Award in Excellence in Clinical Pharmacology), the American College of Clinical Pharmacology (2011

Honorary Fellow), ASCPT (2010 Rawls-Palmer Progress in Medicine Award), and the American Association of Pharmaceutical Scientists (2009 Research Achievement Award in Clinical Pharmacology and Translational Research).

14. I was one of approximately 60 physicians across the country elected to the Association of American Physicians in 2007, and have received awards from multiple institutions for my research accomplishments in medical oncology and clinical pharmacology, including MD Anderson Cancer Center (2008 Emil J. Freireich Award for Clinical Research), the University of North Carolina (2008 Institute for Pharmacogenomics and Individualized Therapy Clinical Service Award), the University of Nebraska (2011 Robert Hart Waldman, M.D. Annual Lecture), the University of Utah (2012 Special Recognition, Department of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy), and The University of Chicago (Arthur H. Rubenstein Mentorship in Academic Medicine Award, Department of Medicine).

15. I am frequently asked to speak at national and international meetings on drug development. Recent examples include FDA meetings (FDA-ASCO Virtual Workshop, May 2022; FDA OCP and ISoP Public Workshop, November 2023) and in sessions (which also included an FDA speaker) at international oncology meetings focused on drug development (EORTC-NCI, AACR, October 2022; ESMO,

October 2023). I was also the keynote speaker at the European Cancer Drug Development Forum Dose Optimization Workshop (April 2023).

16. I have served as a research reviewer for multiple committees and working groups at the NIH, as well as for several cancer societies and state departments of health. I have served as an editor for numerous journals, including the Journal of Clinical Oncology (2001-2007; Associate Editor); Current Pharmacogenomics (2001-2004; Editor-in-Chief); Pharmacogenetics and Genomics (2005 to 2020; Co-Editor-in-Chief); and Clinical Cancer Research (1996-2002; Associate Editor).

17. I have authored more than 500 articles in peer-reviewed journals, many of which concern clinical studies and/or pharmacology of drugs. I am additionally a named inventor on eight issued patents, which include both diagnostic and therapeutic methods for the treatment of cancer.

18. I led multiple studies of irinotecan as detailed in **Appendix A**. (Examples include but are not limited to Original Research Articles 62, 79, 87, 94, 112, 130, 132, 152, 164, and 173). Many of these studies were funded by the National Cancer Institute (NCI), both prior to and after its approval by the FDA in 1996. These studies were the first to demonstrate a relationship between the metabolism of irinotecan and the toxicity of this important drug, leading to our discovery of a common genetic variant (in *UGT1A1*, which encodes an important

drug-metabolizing enzyme) that is associated with the tolerability of patients for irinotecan. This work has been extensively cited and led to multiple patents and patent applications (e.g., U.S. Patent No. 7,807,350) for novel therapeutic and diagnostic strategies, which my employer licensed to Mayo Medical Laboratories in 2005. In addition, we provided data on a study of 66 patients to FDA, for the purpose of describing the risks of irinotecan in patients with reduced UGT1A1 activity in the prescribing information. I also published a detailed summary of this work in 2006. Ratain MJ., "From bedside to bench to bedside to clinical practice: an odyssey with irinotecan." Clin Cancer Res., 12(6):1658-60 (2006).

19. I am a named inventor on U.S. Patent No. 7,807,350, which issued on October 5, 2010, and entitled, "Methods for predicting irinotecan toxicity." The specification illustrates that a POSA understood that the toxicity of irinotecan can be highly variable. Thereafter, I published a paper entitled, "Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the *UGT1A1* genotype of patients with cancer." J Clin Oncol. 32(22):2328-34 (2014). This paper discussed using *UGT1A1* genotyping (i.e., a simple blood test) to determine doses, thereby permitting a higher dose in some patients but requiring a dose reduction in others based on the genotype.

20. Additional information regarding my education, experience, publications, awards and honors, patents, publications, and presentations is detailed in my curriculum vitae (**Appendix A)**.

21. A list of the materials relied upon, in addition to my experience, education, and training, to provide the opinions contained in this declaration is listed below in Section III.

22. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is $1000 per hour. My compensation is not dependent in any way upon the outcome of this matter.

23. I have reviewed the ’552 patent and relevant parts of its prosecution history with the United States Patent and Trademark Office. Specifically, I have reviewed the ’552 patent and its prosecution history in relation to the asserted prior art and arguments at issue in the present IPR.

24. Based on my experience described above and contained in my CV, I have an established understanding of the relevant field in the relevant timeframe and the knowledge that would have been known by a person of ordinary skill in the art (POSA), as defined above and during the relevant time frame (on or before August 21, 2015 – the claimed priority date of the ’552 Patent).

II. SUMMARY OF OPINIONS

25. I have been asked to consider whether claims 1 and 3-15 ("Challenged Claims") of the '552 Patent are obvious in view of the prior art. The Challenged Claims are directed to methods of treating metastatic pancreatic cancer in a human who has not previously been treated with an anticancer agent with a combination of four chemotherapy drugs: (1) 60 mg/m^2 of liposomal irinotecan, (2) 60 mg/m^2 oxaliplatin, (3) 400 mg/m^2 of leucovorin, and (4) 2400 mg/m^2 of 5-fluorouracil.

26. In my opinion, claims 1, 3-6, and 8-14 would have been obvious over Conroy, *et al.*, N. Engl. J. Med., 364(19):1817-25 (2011) ("Conroy" (Ex. 1003)) and Mahaseth, *et al.*, Pancreas, 42(8):1311-15 (2013) ("Mahaseth" (Ex. 1005)) in combination with International Publication No. WO2013/188586A1 ("Bayever" (Ex. 1006)) and the knowledge and skill of a POSA, exemplified by multiple publications regarding liposomal irinotecan, including Saif, Journal of the Pancreas, 15(3):278-79 (2014) ("Saif" (Ex. 1007)), Ko, *et al.*, British J. of Cancer, 109(4):920-25 (2013) ("Ko" (Ex. 1008)), and Cantore, *et al.*, Oncology, 67(2):93-97 (2004) ("Cantore" (Ex. 1009)) and other references discussed herein. My opinions are further supported by post-filing references Nichetti, *et al.*, JAMA Network Open, 7(1):1-13 (2024) ("Nichetti" (Ex. 1010)) and Nevala-Plagemann and Garrido-Laguna, Nature Reviews Clinical Oncology, 21(8):567-68 (2024) ("Nevala-Plagemann" (Ex. 1011)).

27. In my opinion, claims 7 and 15 would also have been obvious in view of the prior art disclosed in ground 1 in view of Masi, *et al.*, Annals of Oncology, 15:1766-72 (2004) ("Masi" (Ex. 1012)) and Ginocchi, *et al.*, Annals of Oncology, 23(9 Suppl.):ix238 (2012) ("Ginocchi" (Ex. 1016)).

28. In my opinion, claims 1 and 3-15 would have been obvious based on the prior art discussed in grounds 1 and 2 and further in view of Carnevale and Ko, Future Oncology, 12(4):453-464 (2016) ("Carnevale" (Ex. 1013)), and/or Dean, *et al.*, J Clin Oncol, 34(4 Suppl.):tps482 (2016) ("Dean" (Ex. 1014)).

29. Finally, I am not aware of any secondary considerations that support non-obviousness of the claims. I reserve the right to address any secondary considerations put forth by Patent Owner (including but not limited to unexpected results) in any later response to this declaration or the petition it accompanies.

III. MATERIALS RELIED UPON

30. I have reviewed the Petition and supporting evidence. I have also reviewed all Challenged Claims of the '552 patent (claims 1 and 3-15), as well as the specification of the '552 patent and relevant parts of its file history, with particular attention to rejections by the Patent Examiner and the responses on behalf of the alleged inventors. I have examined the prior art references asserted against the '552 patent in the Petition. My opinions are based on my own knowledge, experience, and education and with further reference to the exhibits cited herein. I

will use the exhibit numbers listed on the "Table of Exhibits" on pages iii-v of the Petition (Paper 1), which I have included for ease of reference below:

LIST OF EXHIBITS

Exhibit	Description
Ex. 1001	U.S. Patent No. 11,344,552 to Bayever *et al.* ("the '552 patent")
Ex. 1003	Conroy, *et al.*, N. Engl. J. Med., 364(19):1817-25 (2011) ("Conroy")
Ex. 1004	Certified English Translation of the Protocol of Conroy, *et al*, https://www.nejm.org,[1] (2011) ("Conroy Protocol")
Ex. 1005	Mahaseth, *et al.*, Pancreas, 42(8):1311-15 (2013) ("Mahaseth")
Ex. 1006	International Publication No. WO2013/188586 A1 to Bayever ("Bayever")
Ex. 1007	Saif, Journal of the Pancreas, 15(3):278-79 (2014) ("Saif")
Ex. 1008	Ko, *et al.*, British J. of Cancer, 109(4):920-25 (2013) ("Ko")
Ex. 1009	Cantore, *et al.*, Oncology, 67(2):93-97 (2004) ("Cantore")
Ex. 1010	Nichetti, *et al.*, JAMA Network Open, 7(1):1-13 (2024) ("Nichetti")
Ex. 1011	Nevala-Plagemann and Garrido-Laguna, Nature Reviews Clinical Oncology, 21(8):567-68 (2024) ("Nevala-Plagemann")
Ex. 1012	Masi, *et al.*, Annals of Oncology, 15:1766-72 (2004) ("Masi")
Ex. 1013	Carnevale and Ko, Future Oncology, 12(4):453-464 (2016) ("Carnevale")
Ex. 1014	Dean, *et al.*, J Clin Oncol, 34(4 Suppl.):tps482 (2016) ("Dean")
Ex. 1015	U.S. Provisional Application No. 62/208,209 to Bayever *et al.* ("the '209 Provisional")
Ex. 1016	Ginocchi, *et al.*, Annals of Oncology, 23(9 Suppl.):ix238 (2012) ("Ginocchi")
Ex. 1017	Conroy Supplementary Appendix, N. Engl. J. Med., 364(19): 1817-25 Supplementary Appendix (2011) ("Conroy Appendix")

Exhibit	Description
Ex. 1018	Wainberg, *et al.*, Ann Oncol., 3l (Suppl. 3):S241 (2020) ("Wainberg abstract"), corresponding poster ("Wainberg poster"), corresponding presentation ("Wainberg presentation")
Ex. 1019	Wainberg, *et al.*, European Journal of Cancer, 151:14-24 (2021) ("Wainberg 2021")
Ex. 1020	U.S. Non-Provisional Patent Application No. 15/241,106 to Bayever et al ("the '106 Application")
Ex. 1021	Hatachi, *et al.*, Cancer Diagn & Progn, 2(1):101-06 (2022)
Ex. 1022	Zaniboni, *et al.*, Cancer Chemother Pharmacol., 69(6):1641-45 (2012)
Ex. 1023	Tsai, *et al.*, J Gastrointest Oncol., 2(3):185-94 (2011)
Ex. 1024	U.S. Patent No. 8,147,867 to Hong, *et al* ("the '867 patent")
Ex. 1025	Press Release by Merrimack Pharmaceuticals, Inc. on August 1, 2011
Ex. 1026	International Publication No. WO 2016/094402 A1 to Bayever ("Bayever II").
Ex. 1027	Alcindor, *et al.*, Curr Oncol, 18(1):18-25 (2011)
Ex. 1028	U.S. Provisional Application No. 62/216,736 to Bayever *et al*. ("the '736 Provisional")
Ex. 1029	U.S. Provisional Application No. 62/273,244 to Bayever *et al*. ("the '244 Provisional")
Ex. 1030	U.S. Provisional Application No. 62/281,473 to Bayever *et al*. ("the '473 Provisional")
Ex. 1031	U.S. Provisional Application No. 62/302,341 to Bayever *et al*. ("the '341 Provisional")
Ex. 1032	U.S. Provisional Application No. 62/323,245 to Bayever *et al*. ("the '245 Provisional")
Ex. 1033	Leucovorin Calcium Injection Label (2011)
Ex. 1034	Gemcitabine Injection Label (2012)
Ex. 1035	Abraxane Paclitaxel Label (2013)

Exhibit	Description
Ex. 1036	XELODA Capecitabine Label (2000)
Ex. 1037	Camptosar FDA Label (2006)
Ex. 1038	Eloxatin Oxaliplatin Injection Label (2012)
Ex. 1039	Tarceva Erlotinib Tablets Label (2013)
Ex. 1040	Fluorouracil Injection Label (2012)
Ex. 1041	Conroy, *et al.*, Curr Oncol Rep., 15(2):182-9 (2013)
Ex. 1042	Ko, J Clin Oncol, 29(28):3727–29 (2011)
Ex. 1043	Blazer, *et al.*, ASCO Meeting Abstr. 32(Suppl. 3):275 (2014)
Ex. 1044	Alessandretti, *et al.*, ASCO Meeting Abstr. 31 (Suppl. 15): e15176 (2013)
Ex. 1045	Paller, *et al.*, Clin Cancer Res., 20(16); 4210–17 (2014)
Ex. 1046	Hamberg, *et al.*, Eur J Cancer, 46(16):2870-78 (2010)
Ex. 1047	Hess, *et al.*, Annals of Oncology, 21(12):2390-95 (2010)
Ex. 1048	Goel, *et al.*, Anti-Cancer Drugs, 18(3):263-71 (2007)
Ex. 1049	Rachamalla, *et al.*, Anticancer Drugs, 15(3):211-7 (2004)
Ex. 1050	Wildiers, Eur J Cancer, 43(15):2235-41 (2007)
Ex. 1051	Gajra, *et al.*, J Geriatr Oncol, 6(2):133-40 (2015)
Ex. 1052	Shayne, *et al.*, Cancer, 110(7):1611-20 (2007)
Ex. 1053	Sharma, *et al.*, J Clinical Oncology, 32(3 Suppl.): 562 (2014)
Ex. 1054	Chang, *et al.*, Cancer Chemother Pharmacol., 75(3):579-86 (2015)
Ex. 1055	Roy, *et al.*, Annals of Oncology, 24(6):1567-73 (2013)
Ex. 1056	Slingerland, *et al.*, Drug Discov Today, 17(3-4):160-66 (2012)
Ex. 1057	Chen, *et al.*, J Clin Oncol, 26(15 Suppl.):2565 (2008)
Ex. 1058	Kim, *et al.*, Cancer Res., 72(14 Suppl.): A41 (2012)
Ex. 1059	Hann, *et al.*, Cancer Res, 67(9 Suppl.): 5648 (2007)
Ex. 1060	U.S. Non-Provisional Patent Application No. 62/343,313 to Bayever et al (“the ’313 Provisional”)

Exhibit	Description
Exs. 1084 – 1123	File History of U.S. Patent No. 11,344,552 Parts 1 to 40

[1]https://www.nejm.org/doi/full/10.1056/NEJMoa1011923#APPNEJMoa1011923PRO

IV. THE UNDERSTANDING APPLIED TO MY ANALYSIS

31. In preparing and forming my opinions set forth in this declaration, I have been informed by counsel of the relevant legal principles. I applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below. In performing my analysis and reaching my opinions and conclusions, I have been informed of and have been advised to apply various legal principles relating to unpatentability, which I set forth herein. In setting forth these legal standards, it is not my intention to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I am providing.

32. I understand that my opinions regarding unpatentability are presented from the viewpoint of a person of ordinary skill in the art ("POSA" or "skilled artisan") in the field of technology of the patent as of the patent's priority date. In this declaration, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date for the '552 patent, which I have been informed for this proceeding is August 21, 2015. (Ex. 1001 at 2.) To the extent Patent Owner

asserts that the claims of the ’552 patent are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

33. I understand that in an IPR proceeding, claims should be construed as having their ordinary and customary meaning as understood by a POSA at the time of the invention. I understand that claims should be read in the context of the claim language of which they are a part. I further understand that the specification and file history can also inform the scope of the claims. If, after a review of this evidence, the construction is not apparent, I understand that extrinsic evidence, such as dictionary definitions, treatises, and trade journals, may be consulted to discern the meaning of a term. For terms where no construction is necessary, I have simply read the terms according to their ordinary and customary meaning. My understandings herein are made in light of how a POSA in or around 2015 would view the ordinary and customary meaning of the claim terms. I reserve the right to supplement my Declaration should any claim terms be given different constructions.

34. I understand that a limitation can be expressly disclosed by the reference or be inherent. I further understand that for a feature to be inherently disclosed, a POSA would understand the inherent feature would necessarily and inevitably be present when the teaching of the reference is practiced. That is, I understand that if a feature is not necessarily and inevitably present, it is not inherently disclosed.

35. I understand that a patent claim may be unpatentable for obviousness if the difference between the claimed subject matter and the prior art is such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. I understand that a finding of obviousness requires a determination of: (1) the scope and content of the prior art; (2) the difference(s) between the claimed invention and the prior art; and (3) the level of skill of the POSA. I understand this analysis looks at whether the differences are such that the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. I also understand that a patent claim may be unpatentable for obviousness if the prior art discloses a range of doses and there is no evidence that a narrower claimed range (or specific dose) is critical for the operability of the claimed invention.

36. It is my understanding from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a POSA has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. It is my understanding that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason for combining

prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

37. My understanding is that the obviousness inquiry is not limited to just the prior art references being applied, but includes the knowledge and understanding of one of ordinary skill in the art. However, I understand that merely demonstrating that each element, independently, was known in the prior art is, by itself, insufficient to establish a claim was obvious. My understanding is that the test for obviousness is not whether the features of one reference can be incorporated into the structure of another reference, but rather what the combined teachings would have suggested to those of ordinary skill in the art. I further understand that a party seeking to invalidate a patent must show that a POSA would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.

38. I understand that a combination of old, familiar, or known elements according to known methods is likely to be obvious when it does no more than yield predictable results. Predictable variations of a work from one field are likely to be obvious, even if the variation is in another field. For example, where a technique has been used to improve a device, use of the same technique to improve similar devices is a predictable variation and likely obvious. Likewise, if the use of prior art for improvements is simply done according to the prior art's established functions, a POSA has simply implemented a predictable variation. If there existed

at the time of invention a known problem for which there was an obvious solution, a patent claim encompassing that solution is not patentable.

39. I further understand that any obviousness analysis must consider objective evidence of non-obviousness, where such evidence is present. I understand that objective evidence of non-obviousness includes (1) copying, (2) long felt but unsolved need, (3) failure of others, (4) commercial success of the invention, (5) unexpected results created by the claimed invention, (6) unexpected properties of the claimed invention, (7) licenses showing industry respect for the invention, (8) skepticism of skilled artisans before the invention, (9) recognition of invention's advancement, and (10) contemporaneous invention by others or absence thereof. In general, there must be a connection between any of the factors and the claimed invention.

40. I understand that a claim in a granted patent must be sufficiently supported by the original disclosure of the granted patent, read in the context of what one of ordinary skill in the art would have known at the time of the claimed invention. I understand that the basic inquiry for written description is whether the specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention.

41. I also understand that claims must be enabled by the original disclosure of the patent. For the claims to be enabled, the information contained in the

disclosure must be sufficient to inform those skilled in the relevant art how to make and use the claimed invention without undue experimentation. I understand that the enablement requirement is separate and distinct from the written description requirement.

42. I understand that to establish priority to a previously filed patent application, the earlier application must describe the later-claimed invention in sufficient detail that a POSA can clearly conclude that the inventor invented and had possession of each element of the claimed invention as of the earlier filing date being sought. I understand that this requires that the earlier disclosure must describe and enable every limitation of the later-claimed invention.

43. Although the following analysis cites to particular pages, lines, paragraphs, or figures of many of the references discussed, these citations are intended to assist in understanding the various bases of my conclusions, and prior art teachings used to reach them. These citations are not intended to be an exhaustive recitation of every page, line number, or paragraph in which these teachings may be found. Similar teachings or disclosures may be found at other pages, lines, or paragraphs, as well as in other references, and it is to be understood that my opinions and statements are made in view of all of the references and teachings I have reviewed.

V. LEVEL OF ORDINARY SKILL IN THE ART

44. In my opinion, the following definition of a POSA applies to the claims of the ’552 patent.

45. Based on the ’552 patent, a POSA would have been a physician (e.g., M.D. degree) who would have completed training in medical oncology, a pharmacist (e.g., Pharm.D. degree) with oncology experience, and/or a pharmaceutical scientist (e.g., Ph.D. degree with at least 2 years of postdoctoral experience). The POSA would also have experience in gastrointestinal oncology, as well as an understanding of pharmacogenomics. This POSA would have been part of a team of professionals with these credentials and post-doctoral experience.

46. A POSA would have understood the prior art references referred to herein and would have the capability to draw inferences. It is understood that, to the extent necessary, a POSA may collaborate with one or more other POSAs for one or more aspects with which the other POSA may have expertise, experience, and/or knowledge. Additionally, a POSA could have had a lower level of formal education than what I describe here if the person has a higher degree of experience.

47. As shown by the qualifications provided in **Appendix A** and as explained in this declaration, I met the qualifications of a POSA for purposes of the ’552 patent.

VI. CLAIM CONSTRUCTION

48. I understand that claims of a patent subject to IPR should be construed in accordance with the plain and ordinary meaning of such claim as understood by a POSA in view of the specification of the patent and the prosecution history pertaining to the patent.

49. In my opinion, in view of the specification and prosecution history of the '552 patent, the plain and ordinary meaning of "[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," would be understood by a POSA to broadly encompass administration of the recited four-drug regimen for the purpose of alleviating or reducing the symptoms, tumor size, and/or complications associated with metastatic adenocarcinoma of the pancreas or otherwise managing the disease without requiring any specified treatment effect. Specifically, the claims do not require that the treatment regimen be superior to any other standard treatment; simply that the POSA would expect that the treatment regimen be superior to no treatment in some regard. Furthermore, the claims do not require that the treatment regimen be less toxic than any other treatment; thus, a treatment that is toxic but has a potential therapeutic effect would suffice. The claims also do not require that the treatment regimen has been proven to be superior through a randomized clinical trial or otherwise.

50. The terms "treating" and "treat" are well-understood terms in the medical community. Treating a patient is always with the attempt or intent to cause a therapeutic improvement of the patient, which, in the case of metastatic pancreatic cancer, could be reduced tumor growth or increased overall survival in the patient. However, "treatment" does not require a certain level of efficacy, and oftentimes, treating patients with this disease does not result in therapeutic improvement.

51. As noted above, nothing in the claim language for "method of treating" or "to treat the metastatic adenocarcinoma of the pancreas in the human patient" requires that "treating" brings about a particular result, such as a therapeutic improvement in efficacy. Instead, the body of the claims defines the method of treatment with structural components – administering a specific combination of drugs given at specified doses, frequency (every two weeks), and conditions (patients who have not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas).

52. The specification of the '552 patent supports the above construction. For example, in the "Summary" section, the '552 patent states, "Improved antineoplastic therapies for the treatment of pancreatic cancer" and "The improved antineoplastic therapies can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens." (Ex. 1001 at 2:23-25.) While the Summary makes this prophetic statement of superiority to a particular

prior art regimen, none of the claims make any such statement, and there are no data in the specification that would support the prophecy.

53. The specification also states that, "A method of treating pancreatic cancer can comprise the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient," but omitting any requirement of a therapeutic improvement of clinical efficacy. (Id. at 2:26-29.) Consistently, while the specification describes multiple dosing options of this general method, these dosing options are only defined by administration of the drugs and not by any therapeutic result. (Id. at 2:29-46.) A POSA would also understand that the claim does not require any minimum number of treatments, although the limitation "once every two weeks" implies that there would be at least two treatments administered.

54. Similarly, the specification states, "The invention is based in part on the discovery that the administration of a dose of mg/m^2 liposomal irinotecan was not well tolerated in humans when administered in combination with" certain drug regimen, and "Accordingly, the preferred methods of treating (previously untreated) pancreatic cancer provide for the administration of a human tolerated antineoplastic therapy." (Id. at 2:57-65; see also id. at 2:47-56 (describing other bases for invention).) This again supports the above claim construction that "treatment" does

not require actual efficacy, but simply administration of the claimed doses with a therapeutic goal.

55. Additionally, in the "Further Embodiments of Invention," the specification states, "A method of treating pancreatic cancer … the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject." (Id. at 18:32-38.) While the cited sentence uses the phrase "therapeutically effective," the inventors chose not to include this phrase in any of their claims. In addition, Patent Owner used the word "treatment" synonymously with administration or exposure to. For example, the specification states that "FIG. 6A is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after ***treatment with a saline control***…." (Id. at 8:31-36 (emphasis added); see also FIGS. 5A, 5C, 6A-C, and 9 (all showing similar use of the word "treatment")).

56. The patent applications to which the '815 Application and '552 patent claim priority further support this understanding. For example, in the '209 Provisional, to which the '552 patent claims its earliest priority, the specification defines "effective treatment," to mean "treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder." (See Ex. 1015 at¶

[0036].) The ’209 Provisional further states that a beneficial effect can take the form of “an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy” or “arresting, slowing, retarding, or stabilizing of a deleterious progression of a market of a cancer.” (Id.) The ’209 Provisional further states that the term “effective treatment” “may refer to alleviation of at least one symptom of a cancer” or “may, e.g., reduce pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.” (Id.) The ’209 Provisional also states that the disclosure relates to a “method of treatment (e.g., effective treatment) of metastatic pancreatic cancer in a patient.” (Id. at ¶ [0007].) A POSA would understand, especially based on such disclosures in the ’209 Provisional, that the term “treatment” simply implied “administration” (with a desire for a beneficial or therapeutic effect) and that “treatment” included both effective treatment and ineffective treatment.

57. The ’209 Provisional further defines “effective amount” or “therapeutically effective amount” to mean “an amount of an agent that provides the desired biological therapeutic and/or prophylactic result.” (Id. at ¶ [0037].) “That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviating of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.” (Id.) Patent Owner clarifies that

"[i]n reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation." (Id.) The specification provides examples of an effective amount, which include an amount sufficient to (i) delay tumor development; (ii) prevent or delay tumor recurrence; (iii) reduce the number of cancer cells; (iv) reduce tumor size; (v) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (vi) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (vii) inhibit tumor growth; (viii) prevent or delay occurrence and/or recurrence of tumor; and/or (ix) relieve to some extent one or more of the symptoms associated with the cancer. (Id.) A POSA would understand, especially based on such disclosures in the '209 Provisional, that an "effective amount" was one that had been shown to provide one or more of the benefits above.

58. Notably, every provisional application to which the '552 patent claims priority makes this distinction in that they define "effective treatment" and "effective amount" in the same or similar terms as the '209 Provisional and specify that "effective treatment" is just one example of the broader "treatment." (See Ex. 1028, ¶¶ [0007], [0036]; Ex. 1029, ¶¶ [0007], [0041]; Ex. 1030, ¶¶ [0007], [0047]; Ex. 1031, ¶¶ [0007], [0049]; Ex. 1032, ¶¶ [0007], [0051].) Perhaps more notable, while the term "treatment" is used throughout the '552 patent, the term "effective

treatment" is never used the claims (nor are terms like "improved treatment"). (See generally Ex. 1001.)

59. In addition, Patent Owner knew how to claim an effective treatment or effective amount. For example, claim 1 in the '209 Provisional claimed "administering to the subject a **therapeutically effective amount** of MM-398 liposomal irinotecan." (Ex. 1015, claim 1.)

60. A POSA, having reviewed all of these applications, would be confident in understanding that treatment, as used in the claims of the '552 Patent, simply means administration of drugs or therapy with an attempt or intent to cause a therapeutic improvement of or beneficial effect to the patient but with the understanding and knowledge that such an outcome is not required or expected in any particular patient.

VII. BACKGROUND AND STATE OF THE ART

61. In this section, I present a brief overview of the state of the art before the effective filing date of the '552 patent, which relates to the issues discussed in the following sections. Specifically, the patent claims the use of a combination of four well-known drugs (5-fluorouracil ("5-FU"), leucovorin ("LV"), oxaliplatin, liposomal irinotecan) in an established way (e.g., modification of FOLFIRINOX) for an established purpose (first-line treatment of advanced pancreatic cancer). This section is not intended to be technically comprehensive, but rather provides a

foundation for a better understanding of the ’552 patent, the prior art, and certain terminology.

A. Adenocarcinoma of the Pancreas

62. Adenocarcinoma of the pancreas (henceforth referred to as “pancreatic cancer” or “PC”) is a devastating diagnosis and, at the time of the patent filing, the fourth most common cancer-related death in the United States. (Ex. 1005 at 1.)

B. Combination Chemotherapy Was Commonly Used to Treat Pancreatic Cancers

63. Chemotherapy is commonly used for treating pancreatic cancer, either alone or in combination with surgery and/or radiotherapy. For example, by the early 2010s, numerous chemotherapy drugs had been used—alone or in combination—in both first-line and second-line therapies for pancreatic cancer. Of these, there were seven drugs that were commonly prescribed, which included 5-FU, LV, gemcitabine, nab-paclitaxel, capecitabine, irinotecan, and oxaliplatin. (See, e.g., Ex. 1003 at 2, 7-8; Exs. 1033-1040.)

64. Of the aforementioned agents, only three had received FDA approval for the treatment of pancreatic cancer: 5-FU, gemcitabine, and nab-paclitaxel. (Exs. 1034, 1035, 1040.) While the generic drugs oxaliplatin and irinotecan were never approved for this indication, they were well known to POSAs and widely used and prescribed for pancreatic cancer. (See, e.g., Ex. 1003 at 1-2.) In addition, erlotinib (an oral inhibitor of the epidermal growth factor receptor) had been approved for

first-line therapy in combination with gemcitabine but was rarely prescribed for this indication, given its minimal benefit. (Ex. 1039.)

C. FOLFIRNOX Was a Known and Well-Used Treatment But It Had Significant Drawbacks

65. FOLFIRINOX is comprised of four drugs: oxaliplatin (85 mg/m^2 over 2 hours), followed by irinotecan (180 mg/m^2 over 90 min) and LV (400 mg/m^2 over 2 hours), followed by 5-FU (a 400 mg/m^2 bolus and 2,400 mg/m^2 46 hours continuous infusion). (Ex. 1003 at 1; Ex. 1004 at 5.)

66. Prior to the filing of the '815 Application, Conroy compared FOLFIRINOX with gemcitabine in metastatic PC in a randomized phase 3 trial. (Ex. 1003; see also Ex. 1005.) This study showed significant improvements in, among other things, overall survival (11.1 vs. 6.8 months) with FOLFIRINOX compared to gemcitabine. (Ex. 1003 at 1; Ex. 1041 at 3.) Based on this study, FOLFIRINOX was considered the most effective regimen for metastatic pancreatic cancer, and it emerged as the new standard of care in appropriate patients with a good performance (i.e., functional) status. (Ex. 1041 at 1.)

67. However, FOLFIRINOX had its drawbacks, including the potential for life-threatening (and even fatal) toxicity, yet with only a small proportion of patients surviving even two years. (Ex. 1003, FIG. 1A; Ex. 1041, Table 1.) For example, FOLFIRINOX was associated with high rates of severe and life-threatening diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory

neuropathy. (Ex. 1003 at 8; Ex. 1041 at 3; Ex. 1042 at 1.) Given these toxicities, a POSA was motivated to modify FOLFIRINOX. In fact, modifications to FOLFIRINOX were common. (See, e.g., Ex. 1041, Ex. 1042.)

D. A POSA Understood How To Create Different Combination Regimens

68. FOLFIRINOX had been developed because all the component drugs were commonly used in several gastrointestinal malignancies. (See, e.g., Ex. 1041 at 2; Ex. 1009 at 1-4; Ex. 1012; see also Section VII.B.) This regimen was built on other well-known combinations, and furthermore, the FOLFOXIRI regimen had also been developed (for colorectal cancer) using the exact same components as in FOLFIRINOX. (Id.)

a. A POSA Regularly Modified FOLFIRINOX Doses

69. It was frequently necessary to reduce the doses of the drugs in the FOLFIRINOX regimen. For example, the median dose intensity of FOLFIRINOX delivered in the experimental arm was only 80% overall and varied by drug: 5-FU, 82%; irinotecan, 81%; oxaliplatin, 78%; gemcitabine, 100%. (Ex. 1003 at 4.) That is, a POSA would understand that many patients received a dose less than the prescribed dose for 5-FU, irinotecan, and oxaliplatin and/or that doses delayed due to toxicities. A POSA would therefore have been motivated to avoid toxicity by using lower doses of one or more chemotherapy drugs. Such efforts were widely practiced. (See, e.g., Ex. 1041.)

70. At the time of the '815 Application, several modifications of FOLFIRINOX, had been reported with an aim to improve its toxicity profile. (See, e.g., Ex. 1005 (removing 5-FU bolus, which had less grade 3-4 toxicity but similar activity); Ex. 1041.)

71. A POSA was also motivated to reduce the dose of irinotecan and oxaliplatin, either at the start of treatment or after observing toxicities. (See, e.g., Ex. 1041 at 4-5(discussing and citing multiple examples of studies—from respected institutions—with reduced doses); Ex. 1043.)

72. At least for frail and elderly patients, additional adjustments had been made. For instance, in a series of 19 patients over age 65, the bolus of 5-FU was dropped and doses of both oxaliplatin and irinotecan were lowered (5-FU 2000 mg/m^2 over 46 h, oxaliplatin 50 mg/m^2, irinotecan 135 mg/m^2). (Ex. 1044 at 1.)

b. POSAs Regularly Created Other Combination Regimens Based on The Standard Chemotherapy Drug Options

73. In addition, and as discussed above, all the components of the FOLFIRINOX regimen (infusional 5-FU, LV, irinotecan, and oxaliplatin) had been in widespread clinical use since 2002 (the year of approval of oxaliplatin). As apparent from the discussion of the drug regimens above, combinations of these drugs were widely prescribed for gastrointestinal malignancies, including pancreatic cancer. In fact, Patent Owner admits that oxaliplatin is "typically used in combination with infusional 5-FU/LV." (See, e.g., Ex. 1015 at ¶ [00209].)

74. Thus, a POSA had extensive knowledge regarding each of the drugs in the FOLFIRINOX regimen, alone and in combination, given that each of them was approved for the treatment of colorectal cancer. (Exs. 1033, 1037, 1038, 1040) As it was standard oncology practice to administer chemotherapy drugs in combinations, rather than as single agents, a POSA had extensive experience using combinations of these same components and had developed a variety of regimens, including but not limited to IFL, FOLFIRI, FOLFOX, and FOLFOXIRI. This was a typical practice of a POSA, modifying drug regimens to develop new treatments.

75. Furthermore, FOLFOX (oxaliplatin, 5-FU, and LV) and FOLFIRI (irinotecan, 5-FU, LV) had been evaluated in clinical trials for the treatment of pancreatic cancer. (See, e.g., Ex. 1003 at 2; Ex. 1041 at 2.)

76. Likewise, based on a finding that oxaliplatin and irinotecan "have shown cytotoxic synergisms *in vitro* and *in vivo*, with no overlapping toxicity," Cantore et al. published a study of a combination chemotherapy treatment for pancreatic cancer consisting of 60 mg/m^2 oxaliplatin and 60 mg/m^2 irinotecan. (Ex. 1009 at 1-5 (finding the treatment an "active and well-tolerated combination in patients with advanced pre-treated pancreatic cancer.").)

c. When Creating a New Combination, a POSA Understood Dose Reductions to Be Common Practice

77. Dose reduction in chemotherapy is a common and well-established practice across a wide range of cancer types and treatment regimens. Thus, a POSA

is highly skilled in reducing chemotherapy doses to mitigate adverse events, either preemptively or after a prior dose based on unacceptable toxicity. A POSA was very familiar with the need to consider lower doses when developing new combinations of known drugs, since the POSA would not expect that all drugs can be administered safely at their standard doses. (See Ex. 1045.) While a POSA would have been motivated to administer the maximal tolerated dose of a combination, a POSA would understand that there were an infinite number of maximal dose combinations. (See Ex. 1046.) As a practical matter, a POSA fixed the dose of one or more drugs in a combination, and then used routine experimentation to define one or more maximally tolerated dose combinations. (See, e.g., Exs. 1047-49.)

78. Based on the disclosures in the prior art, a POSA would have understood that doses of oxaliplatin in the range of 60-85 mg/m^2 were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m^2 FOLFIRINOX dose. A POSA would have used routine experimentation to determine a maximally tolerated combination of 5-FU, LV, oxaliplatin and liposomal irinotecan. (See, e.g., Section VII.D.a-b.) Because most dosing is done in increments of 5 mg/m^2, a POSA would have a limited number of tolerable doses to choose from and found any oxaliplatin dose within the range of 60-85 mg/m^2 to be obvious considerations. In addition, a POSA would have been aware of the 60 mg/m^2 dose of oxaliplatin disclosed in the Conroy protocol for

patients who had already experienced toxicity. (See Section VIII.B.) A POSA would have been motivated to select a dose, such as 60 mg/m^2 that had already been demonstrated to be effective in a similar context (e.g., FOLFIRINOX for pancreatic cancer). (See id; see also Section VII.D.b (also disclosing a 60 mg/m^2 dose of oxaliplatin).)

79. Oncologists often reduce chemotherapy doses preemptively based on clinical judgment, considering factors such as age, treatment intent, comorbidities, and the toxicity of chemotherapeutic agents, as supported by various studies. (See Ex. 1050; Ex. 1051; Ex. 1052.) A POSA would also be aware that genetics can impact the toxicity of FOLFIRINOX and reduce the irinotecan dose accordingly. (See Ex. 1053 (describing relationship of *UGT1A1*28* allele genotyping to irinotecan toxicity); Ex. 1041 at 4 (stating that "deletion of bolus 5-FU and dose reduction of irinotecan, owing to the presence of the UGTA1*28/28 genotype, were the commonest modifications").)

80. Preemptive dose reductions are also common when the treatment intent is palliative rather than curative. Particularly in the setting of incurable metastatic disease, the focus shifts to minimizing toxicity and improving quality of life, which often leads oncologists to favor dose reductions. (Ex. 1050 at 2.) Indeed, a retrospective study found that 25% of 321 patients treated with palliative intent chemotherapy received preemptive dose reductions, compared to 15% of patients

who received preemptive dose reductions in the curative setting. (See Ex. 1051 at 1, 4.) Comorbid conditions, such as diabetes, heart disease, and a history of prior cancers, also influence the decision to reduce the dose preemptively. (See id. at 4.)

81. Additionally, preemptive dose reductions are commonly observed in patients receiving platinum-containing regimens, such as oxaliplatin. A prospective study of 976 patients treated for common malignancies revealed that significantly more preemptive dose reductions occurred with platinum-based regimens compared to taxane- and anthracycline-based regimens (41.3% vs. 33.9% vs. 16.4%). (See Ex. 1052 at 4.)

82. Unplanned dose reductions are typically initiated in response to chemotherapy toxicity, which affects a significant portion of patients, making a POSA experienced in adjusting dosage to manage side effects. One study evaluating treatment characteristics that contribute to hematologic toxicity found that 51.1% of 657 patients experienced major reductions in actual dose intensity, with the mean relative dose intensity at 80%. (See Id.)

E. A POSA Would Have Understood That Liposomal Irinotecan May Be Superior To Irinotecan

83. At the time of the '552 patent, a POSA would have been aware of both irinotecan (also known as free irinotecan, CPT-11, or Camptosar) and liposomal irinotecan and understood that liposomal irinotecan may be superior to irinotecan.

84. There had been a long history of using liposomes to try to improve the therapeutic index of cancer chemotherapy. (Ex. 1056.) While preclinical studies often suggested improved antitumor efficacy and tolerability, there was no clear evidence that such formulations were superior to unencapsulated drugs.

85. Onivyde (previously known as MM-398) is one of several liposomal irinotecan formulations that had been evaluated for the treatment of cancer. (Ex. 1054 at 7.) MM-398 is an irinotecan octasulfate salt liposome injection, also described as a nanoliposomal encapsulation of irinotecan. (Ex. 1008 at 2.) MM-398 is also known as PEP02 or nal-IRI, as described in U.S. Patent No. 8,147,867. (Ex. 1006 at 9; Ex. 1024.) It is also referred to as irinotecan HCl liposome injection because irinotecan HCl is the active pharmaceutical ingredient that is used to load irinotecan into liposomes containing triethylammonium sucrose octasulfate to prepare MM-398 liposomes. (Ex. 1006 at 5.) During the encapsulation process, hydrochloride ions of the irinotecan HCl react with the triethylammonium ions of the triethylammonium sucrose octasulfate to yield triethylammonium chloride (triethyl amine hydrochloride), leaving irinotecan sucrose octasulfate salt as the entrapped pharmaceutical agent within the MM-398 liposomes. (Id.)

86. An MM-398 liposome is a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. (Ex. 1006 at 9.) MM-398 has a

diameter of approximately 80-140 nm and contains distearoylphosphatidylcholine (DSPC), cholesterol (Chol), and N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE) (prepared from poly(ethylene glycol) with molecular weight 2,000) were co-dissolved in chloroform in a molar ratio of 3:2:0.015. (Id.; Ex. 1024 at 27:46-51; 91:13-18.) MM-398 can be diluted in 500mL of 5% dextrose injection USP and infused over a 90-minute period. (Ex. 1006 at 9.)

87. The metabolic transformation of MM-398 to SN-38 (e.g., in plasma) includes two steps: (1) the release of irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. (Ex. 1006 at 11.) Once irinotecan is released from the liposomes, irinotecan is catabolized by the same metabolic pathways as conventional (free) irinotecan. (Id.) Therefore, a POSA would have expected that the genetic polymorphisms in humans predictive of the toxicity of irinotecan would also be important for MM-398 similar. (Id.)

88. Patent Owner admits that prior to the filing date of the first provisional application to which the ’552 Patent claims priority, liposomal irinotecan (or at least Nal-IRI, aka MM-398) had been studied in multiple clinical trials in patients, including those with metastatic pancreatic cancer. (See Ex. 1015 at ¶ [00203], Table 3 “Summary of Clinical Studies with Nal-IRI.”) The ’209 Provisional notes that “[n]ine clinical studies of nal-IRI have been completed to date, with over 400

patients across multiple tumor types exposed to various dosing regimens, with an additional three studies actively recruiting patients across multiple tumor types (see Table 3)." (Id. at ¶ [00223] (noting studies were on patients with cervical, gastric, pancreatic, and colorectal cancer, and others).) As exemplified by this disclosure, a POSA at the time would have known that cancer drugs used to treat one cancer type were often considered as options to treat other cancers.

89. The first clinical results for MM-398 were disclosed in 2008. (Ex. 1057.) Notably, of the 11 patients reported (who received doses of 60-180 mg/m^2), one died secondary to diarrhea and neutropenia. Multiple other clinical trials had been completed prior to the filing of the '552 patent application, including one randomized trial in esophageal/gastric cancer, comparing MM-398 to both docetaxel and irinotecan. (See Ex. 1055.)

90. On May 1, 2014, Merrimack Pharmaceuticals, Inc. (Cambridge, MA, USA) announced the results of the NAPOLI-1 study in previously treated APC, in which the combination of MM-398 with 5-FU and LV achieved an overall survival of 6.1 months, a 1.9-month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and LV alone. (Ex. 1007.) Notably, this study did not compare the combination to the established FOLFIRI regimen, which contains free irinotecan instead of MM-398.

91. However, preclinical studies of MM-398 suggested it was superior to irinotecan. For example, MM-398 was known to have an extended plasma half-life and higher intratumoral deposition compared with free irinotecan. (Ex. 1058; Ex. 1008 at 2, 5.) MM-398 also demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model. (Id.; Ex. 1059; Ex 1006 at 25.)

VIII. OVERVIEW OF KEY PRIOR ART AND STATE OF THE ART REFERENCES

92. Prior to the filing of the ’815 Application, a POSA would have known that the treatments available for pancreatic cancer carried severe toxicity concerns, e.g., in elderly. In addition, the treatments available were not curative but could only prolong the life of a patient by a matter of months, but at the cost of a significant impact on the patient’s quality of life due to drug toxicities and frequent visits to the oncologist. Thus, the choice of drugs and dosages was constrained by the known toxicity risks, and the patients’ willingness to accept such risks. A POSA would have understood the simplest way to address toxicity concerns was (and still is) to lower the dosage of toxic drugs administered to the patient. Such an approach was, at the time of the filing of the ’552 patent and is still today, standard in oncology. This approach was (and is) always considered throughout a patient’s treatment course, especially in treatment settings that were not curative, such as metastatic pancreatic cancer.

93. Other known options that were being studied or suggested were modifying known treatments, including those used to treat the same disease (pancreatic cancer) or similar diseases (such as other types of cancer). For example, a POSA would have been aware of FOLFIRINOX because of its efficacy, but would have also been wary of the toxicities associated with the regimen. As a result, a POSA would have been motivated to modify FOLFIRINOX by reducing the dosages of one or more drugs. (See, e.g., Ex. 1041; supra Section VII.D.) As mentioned above, dosage changes to address toxicity concerns were a regular activity and skill set of a POSA. In addition, a POSA would have been aware of liposomal irinotecan as an alternative to irinotecan. (Supra Section VII.E.) In fact, as further described below, Patent Owner admits that liposomal irinotecan was being studied as a treatment for multiple cancers prior to any application to which the '552 patent claims priority.

A. Conroy (Ex. 1003)

94. Conroy et al., entitled "FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer," was published in the New England Journal of Medicine on May 12, 2011 (Ex. 1003). I understand that Conroy is prior art at least because it was a printed publication before the earliest possible filing date of the '815 Application. In addition, Conroy was cited as prior art by the Examiner in

multiple office actions during the prosecution of the ’815 Application, which Patent Owner did not contest. (See generally Exs. 1084, 1088, 1097, 1119.)

95. Conroy discloses the FOLFIRINOX regimen consisting of 85 mg/m^2 oxaliplatin given as a 2-hour intravenous infusion, 180 mg/m^2 irinotecan given as a 90-minute intravenous infusion, 400 mg/m^2 LV given as a 2-hour intravenous infusion, and 5-FU, first administered as a 400 mg/m^2 bolus and then 2400 mg/m^2 5-FU infusion given as a 46-hour continuous infusion, administered every two weeks in first-line therapy in patients with metastatic pancreatic cancer. (Ex. 1003 at 1.)

96. Conroy compares this FOLFIRINOX regimen against gemcitabine at a weekly dose of 1000 mg/m^2 in patients where the primary endpoint was overall survival. (Id. at 1, 3.)

97. Notably, Conroy discloses that “[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.” (Id. at 4.) A POSA would understand that the median relative dose intensity is a way to describe what percentage of the dose identified in the formal regimen was given to a typical patient. Because these represent the doses received by the typical patient, a POSA would understand that some patients received more than, while other patients received less than, the identified median relative dose intensities. Thus, this would suggest to a POSA that a typical patient

received a dose equivalence of less than the prescribed doses for fluorouracil, irinotecan, and oxaliplatin.

98. Conroy reported that with the above median relative dose intensities, the median overall survival was 11.1 months in the FOLFIRINOX group. (Id. at 1, 5.)

99. However, Conroy states that, "The safety profile of FOLFIRINOX was less favorable than that of gemcitabine." (Id. at 8.) In particular, Conroy noted that "FOLFIRINOX was associated with a higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia." (Id.)

100. Conroy's conclusion is that "FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma," despite its safety profile/adverse effects. (Id. at 6.)

101. Conroy also reported that in the study for second-line therapy comparing the FOLFIRINOX regimen to gemcitabine, there was no difference in median survival between the FOLFIRINOX group and the gemcitabine group (4.4. months in each group). (Id. at 5.) A POSA would not find this surprising. A POSA would understand that second-line patients had already received a prior round of chemotherapy or cancer treatment that failed, meaning the cancer was not eliminated and likely continued to progress. A POSA would understand that the prior round of

chemotherapy treatment and progressing cancer would mean that not only was the patient physically weakened (malnourished, fatigued, weakened immune system, etc.) but the cancer being treated had likely mutated and was therefore less susceptible to treatments.

102. Following Conroy's publication, the FOLFIRINOX regimen for first-line therapy in metastatic pancreatic cancer patients became a standard of care. (*See*, e.g., Ex. 1021 at 1-6.)

103. A POSA would have been very familiar with the FOLFIRINOX regimen at the time of the alleged invention and aware of studies on the efficacy, safety, and tolerability of FOLFIRINOX and modifications thereto.

B. Conroy Protocol (Ex. 1004)

104. Conroy Protocol is the clinical trial protocol that was published on-line in conjunction with Conroy. In fact, Conroy noted that "[t]he protocol, including the statistical analysis plant, is available with the full text of this article at NEJM.org" and that "[t]he first author vouches for the fidelity of the study to the protocol." (Ex. 1003 at 3.) I understand that the Conroy Protocol is prior art at least because it was published along with Conroy in 2011 before the earliest possible claimed priority date of the '815 Application.

105. Conroy Protocol discloses that the oxaliplatin dose should be reduced from 85 mg/m^2 to 60 mg/m^2 based on various known toxicities. (Ex. 1004 at 16-18.)

As noted above, a POSA would understand that such dose reductions were standard medical practice. These oxaliplatin dose reductions to 60 mg/m^2 are also consistent with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m^2 dose and indicate that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m^2 based on various toxicity events.

106. In addition to the Conroy Protocol, a "Supplemental Appendix" was also provided and published as part of the supplemental materials with Conroy (Ex. 1017). This Supplemental Appendix also discloses using 60 mg/m^2 oxaliplatin. (Ex. 1017 at 3-7.)

C. Mahaseth (Ex. 1005)

107. Mahaseth et al., entitled "Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma," was published in Pancreas in November 2013 (Ex. 1005). I understand that Mahaseth is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

108. Mahaseth recognized that the "high [response rate] observed with FOLFIRINOX in metastatic disease raises the possibility of using this regimen in earlier-stage disease to downstage tumors for resection." (Ex. 1005 at 1.) A POSA would understand this to mean that because more cancers responded to

FOLFIRINOX as a treatment, it could be used to treat early-stage cancers to shrink them prior to surgery, whereby the tumor would be removed.

109. Therefore, recognizing that FOLFIRINOX has "superior activity" but "increased toxicity," one of Mahaseth's objectives was to address toxicity concerns with FOLFIRINOX. (Id. at 1.) As discussed above with respect to Conroy, this was a known concern with FOLFIRNOX and something those in the art were actively working to address, including Mahaseth. (See id.)

110. Based on the understanding that the "bolus 5-FU contributes to the toxicity," Mahaseth investigated a modified FOLFIRINOX regimen in both locally advanced unresectable and metastatic pancreatic cancer patients by discontinuing the 400 mg/m^2 bolus of 5-FU. (Id.) As discussed herein, a POSA would have known that lowering dosages was a common strategy to remedy or address toxicity concerns. The modified FOLFIRINOX regimen in Mahaseth included oxaliplatin 85 mg/m^2 in water with 5% dextrose intravenously (IV) over 2 hours, LV 400 mg/m^2 in normal saline IV over 90 minutes concurrently with irinotecan 180 mg/m^2 in normal saline IV over 90 minutes, and 5-FU 2400 mg/m^2 in water with 5% dextrose via continuous intravenous infusion over 46 hours. (Id. at 2.) These are the same doses administered in the traditional FOLFIRNOX regimen, with the exception of the 400 mg/m^2 5-FU bolus. (Id.) In the study, the premedication regimen consisted of intravenous serotonin 5-HT3 receptor antagonists and dexamethasone (in

accordance with standard medical practice). (Id.) Patients received a median of 3 cycles of treatment. (Id. at 3.)

111. Mahaseth observed that this "modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC (pancreatic cancer)." (Id. at 1, 5.)

112. First, Mahaseth observed an improved safety profile, when compared to the original FOLFIRINOX regimen, with respect to neutropenia, fatigue, and vomiting. (Id.) Based on the study outcomes, Mahaseth concluded, "Overall modified FOLFIRINOX was safe." (Id.)

113. Second, Mahaseth confirmed that by eliminating the 5-FU bolus, and thereby decreasing the dosage of 5-FU by 400 mg/m^2, the modified regimen improved on FOLFIRINOX's overall efficacy. (Id. at 4.) For instance, Mahaseth found that the modified regimen resulted in progression-free survival (PFS) of 13.7 months and overall survival (OS) of 17.8 months. (Id.) That is an improvement of 7.3 months (PFS) and 6.7 months (OS), respectively.

D. Bayever (Ex. 1006)

114. Bayever et al., entitled "Methods for Treating Pancreatic Cancer using Combination Therapies Comprising Liposomal Irinotecan," is an International Application published under the Patent Cooperation Treaty (PCT) with an International Publication No. WO 2013/188586 A1 and publication date of

December 19, 2013. The inventors are listed as Eliel Bayever, Navreet Dhindsa, Jonathan Basil Fitzgerald, Peter Laivins, Victor Moyo, and Clet Niyikiza. (Ex. 1006 at 1.) Bayever and Fitzgeral are the same named inventors of the '552 Patent. (See Ex. 1001.) I understand that Bayever is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

115. In addition, Bayever was cited as prior art by the Examiner in multiple office actions during the prosecution of the '815 Application, which Patent Owner did not contest. (See generally Exs.1084, 1088, 1091, 1097, 1098, 1119.)

116. Bayever, published after Conroy, and recognizes that "[c]ombination therapies including folinic acid (leucovorin or levoleucovorin), 5-[FU], and irinotecan (FOLFIRI), folinic acid, 5-[FU], irinotecan and oxaliplatin (FOLFIRINOX), or less commonly, a combination of folinic acid, 5-[FU], and oxaliplatin (FOLFOX) are [] used to treat some pancreatic cancers." (Ex. 1006 at 2.) However, Bayever notes various concerns with current treatments, including the toxicity concern related to use of irinotecan. (See id. at 2-3.)

117. Bayever proposes and describes treating pancreatic cancer in a human patient by administering "liposomal irinotecan (i.e., irinotecan sucrose octasulfate salt liposome injection, also referred to as "MM-398") alone or in combination of 5-fluorouracil (5-FU) and leucovorin (together, 5-FU/LV)." (Id. at 4.) Bayever indicates that MM-398 is an irinotecan sucrose sulfate liposome injection and is also

known as PEP02, as described in the '867 patent. (Id. at 9.) The irinotecan sucrose sulfate liposome contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypoly ethlyeneglycol-2000)-1,2-distearoly-sn-glycero-3-phospho-ethanolamine (MPEG-2000-DSPE). (Id.; Ex. 1024 at 27:46-51, 91:13-18, claim 31.)

118. In one example, Bayever describes administering MM-398 at a dose of 80 mg/m^2 administering LV at a dose of 200 mg/m^2 (*l* form, or levoleucovorin) or 400 mg/m^2 (*l* + *d* racemic form) and administering 5-FU at a dose of 2400 mg/m^2 every 2 weeks. (Ex. 1006 at 4.) However, Bayever also discloses that for patients homozygous for the *UGT1A1*28* allele, the MM-398 dose should be lowered to 60 mg/m^2. (Id.; see also id. at claim 3.) Thus, Bayever discloses administering liposomal irinotecan in the range of 60-80 mg/m^2. This disclosure would imply to a POSA that, unless genotyping is performed, dosing of liposomal irinotecan should not exceed 60 mg/m^2, even in the absence of oxaliplatin.

119. Bayever also discloses a phase 3 clinical trial protocol, in which a dose of MM-398 was reduced to 60 mg/m^2 for the first occurrence of grade 3 or 4 adverse event or febrile neutropenia for patients not homozygous for *UGT1Al*28* (Arm C). (Id. at 26-27, 39-42.) This is the same liposomal irinotecan dose as in the Challenged Claims. (Id.)

120. Bayever discloses that "there was a 20-fold increase in tumor AUC_{SN-38} for MM-398 as compared to free irinotecan," and "[t]he long duration of exposure allows for prolonged exposure of the slow proliferating cancer cells to the active metabolite as they progress through the cell cycle." (Id. at 20.) Bayever hypothesized that this activity "result[ed] from a reduction in intra-tumoral hypoxia, and the subsequent downstream effects on angiogenesis, metastasis, and the immunosuppressive environment in tumors." (Id.)

121. Bayever described the advantages of MM-398 as follows:

> This stable liposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process. The long circulating pharmacokinetics and high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR allows for deposition of the liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor**.**

(Id. at 10; see also FIGS. 1-2.)

122. Notable in the passage above, Bayever describes the liposomal irinotecan as having "several attributes that may provide an improved therapeutic index" and allows for "reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor." (Id. at 10.) A POSA would understand this to mean MM-398 could have a superior benefit-risk profile as compared to irinotecan. (See also Section VII.E.)

123. Bayever discusses administering a treatment of liposomal irinotecan (MM-398), LV, and 5-FU, "wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks starting on day 1 and that patients were to be treated "until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination." (Id. at 6, 14, 15, 26-27.) A POSA would understand that a 2-week cycle starting on day one corresponds to treatment being administered on days 1 and 15, as used in the FOLFIRINOX regimen.

124. Bayever notes that the MM-398 can be administered as an infusion over 90 minutes or over 60 minutes, (id. at 5, 6, 13, 26-27, 33 and claims 6, 15), that "5-FU is administered intravenously over 46 hours" and "leucovorin is administered intravenously over 30 minutes," (id. at 5, 6, 13, 26, 55). Bayever states the "MM-

398 PK parameters were not significantly changed when combined with 5-FU/LV." (Id. at 21.)

125. Bayever also provides instructions as to the timing of the administrations of the various drugs. For example, it states that "liposomal irinotecan can be simultaneously administered with 5-FU and leucovorin or [a]lternatively, liposomal irinotecan can be administered in combination with 5-FU and leucovorin, wherein liposomal irinotecan, 5-FU and leucovorin are formulated for separate administration and are administered concurrently or sequentially." (Id. at 14.) A POSA would understand that liposomal irinotecan can therefore be administered simultaneously with or separately (e.g., sequential administration) from 5-FU and LV. Bayever discloses that when sequentially administered "liposomal irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the 5-FU and leucovorin. Such concurrent or sequential administration preferably results in liposomal irinotecan, 5-FU, and leucovorin being simultaneously present in treated patients." (Id.)

126. However, Bayever also discloses that in each cycle, the liposomal irinotecan is administered prior to the LV, and the LV is administered prior to the 5-FU. (Id. at 13, 14, 33 and claim 4.) Bayever further states "leucovorin should always be administered prior to 5-FU." (Id. at 27 and claim 4.) A POSA would therefore understand that liposomal irinotecan can be administered prior to 5-FU and LV

and/or LV likely should be administered prior to 5-FU, as used in the FOLFIRI regimen.

127. Bayever discloses this order of administration of the drugs because "MM-398 modifies the tumor microenvironment in a manner that should make tumors more susceptible to agents such as 5-FU/LV, through decreasing tumor hypoxia and increasing small molecule perfusion," and "hypoxia is a hallmark of resistant and aggressive disease, a reduction in hypoxia is expected to make tumor cells more sensitive to chemotherapies." (Id. at 20, 21.)

128. Bayever also disclosed various differences in MM-398 and free irinotecan, noting that MM-398 had a 2-3 fold higher total irinotecan half-life than free irinotecan, that most irinotecan remained encapsulated in the liposomes during circulation—which would be understood to help better target the cancer while limiting toxicity, and that the MM-398 PK parameters were not significantly changed when combined with 5-FU/LV. (Id.)

129. Bayever states that, "the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy" and "treating the patient results in a positive outcome, wherein the positive outcome is pathologic complete response (pCR), complete response (CR), partial response (PR) or stable disease (SD)." (Id. at 5, 16.) Therefore, a POSA would understand that the

combination treatment proposed in Bayever was expected to be therapeutically effective, consistent with the POSA's understanding of the FOLFIRI regimen.

130. I am aware that the Patent Owner, during prosecution of the '851 Application, argued that Bayever was limited to treating pancreatic cancer only as a second-line therapy. (Ex. 1119 at 146.) Patent Owner stated that "Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® (irinotecan liposome rejection), 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 cancer." (Id. (emphasis in original).) Patent Owner then continued to argue that the POSA would not combine teachings regarding first-line cancer treatments and second-line cancer treatments. (*See id.*) Contrary to these arguments, a POSA would not understand Bayever to be limited to a second-line therapy and would further understand that the disclosures of Bayever contradict this assertion.

131. First, the Background of Bayever states then-current cancer therapies for pancreatic cancer included the first-line therapy of FOLFIRINOX and single agent gemcitabine. (Ex. 1006 at 2-3.) It describes these treatments as the "current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma." (Id.) It also identifies a protein tyrosine kinase inhibitor targeted to EGFR that has "been approved for first-line use in advanced pancreatic cancer."

(Id.) Bayever then states there is an "urgent need for improvements in, and effective alternative to, current therapies for pancreatic cancer" and that its disclosure "addresses this need and provides other benefits." (Id. at 3-4.) A POSA would have understood, from Bayever, that it was attempting to address concerns with known treatments, including first-line treatments, and that it in fact does "address[] this need."

132. Accordingly, a POSA would understand Bayever also describes various embodiments of methods of treatment that are not limited to only second-line therapy. Indeed, a POSA would understand that Bayever was more broadly directed to the treatment of pancreatic cancer. Under the Patient Populations section, Bayever notes that in some embodiments, the patients are those who have already been treated with chemotherapy, gemcitabine, etc. (Id. at 13.) A POSA reading this would understand Bayever to include, but not be limited to, second-line treatment. In addition, Bayever states that, "the pancreatic cancer of the patient undergoing treatment is advanced pancreatic cancer, which is a pancreatic tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor." (Id. at 13.) Indeed, Bayever further states that, "[t]he compositions and methods disclosed herein are useful for the treatment of **all pancreatic cancers**, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments." (Id. (emphasis added).) A POSA reading this, especially in connection with what

Bayever states is the problem addressed above, would understand Bayever also to include first-line treatments. Thus, Bayever defines the patient population as including, but not limited to, patients treated with second-line therapy. Indeed, Bayever provides four examples of second-line therapy before noting two treatment options that do not include prior treatment, i.e., that treatment could be used on patients with "advanced pancreatic cancer" and/or "for the treatment of all pancreatic cancers." (Id.) This passage strongly suggests to a POSA that first-line treatments were within the gambit of Bayever's disclosures.

133. For example, the first paragraph of Bayever's Summary section states, "[p]rovided are methods for treating pancreatic cancer **in a patient** (i.e., a human patient) comprising administering to **the patient** liposomal irinotecan (e.g., irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398) alone or in combination with 5-fluorouracil (5-FU) and leucovorin (together, 5-FU/LV), according to a particular clinical dosage regimen." (Id. at 4 (emphasis added).) A POSA would understand that the methods are not contingent on patient's refractory to a prior cancer treatment. Another example of such a method, without limiting to second-line therapy, is reproduced below:

> In another aspect, a method for treatment of pancreatic cancer in **a patient** is provided, the method comprising co-administering to **the patient** an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one

> cycle of administration, wherein the cycle is a period of 2 weeks, and wherein for each cycle:
>
> (a) liposomal irinotecan is administered to patients not homozygous for the UGTlAl *28 allele on day 1 of each cycle at a dose of 80 mg/m^2, and to patients homozygous for the UGTlAl *28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m^2 to 80 mg/m^2 (e.g., 60 mg/m^2 or 70 mg/m^2 or 80 mg/m^2);
>
> (b) 5-FU is administered at a dose of 2400 mg/m^2; and
>
> (c) leucovorin is administered at a dose of 200 mg/m^2 (l form, or levoleucovorin) or 400 mg/m^2 (l+d racemic form).

(Id. (emphasis added))

134. Furthermore, under Combination Therapy (Section VI), Bayever goes on to describe various combinations of MM-398, dose adjustments, and dosing orders, but never limits the combinations to second-line therapy. (Id. 14.) Similarly, under Treatment Protocols (Section VII), Bayever describes various treatment combinations but again never once limits these protocols to second-line therapy. (Id. at 15.) Moreover, six out of seven working examples, including *in vivo* tumor modeling and Phase I Dose Escalation Studies are not limited to second-line therapy. (Id. at 19-25.) While in a single example, Bayever discloses a proposed Phase III clinical trial study design for second-line therapy for pancreatic cancer patients, a POSA in view of the totality of Bayever's disclosure would have known that the

disclosed methods were not intended to be nor were they actually limited to second-line therapy.

135. Finally, it is worth noting that the publication of Bayever contains 27 claims, none of which are limited to second-line therapy for pancreatic cancer. In particular, claim 3, as reproduced below, covers the same combination of claimed drugs at the same claimed doses as the claims of the '552 patent, except for the claimed oxaliplatin dose, and contains no limitation that requires it be used as a second-line therapy for metastatic pancreatic cancer.

> 3. A method of treating pancreatic cancer in a human patient, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle:
>
> (a) **liposomal irinotecan** is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of **60 mg/m^2** and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;
>
> (b) **5-FU** is administered at a dose of **2400 mg/m^2**; and
>
> (c) **leucovorin** is administered at a dose of **200 mg/m^2 (*l* form)** or **400 mg/m (*l* + *d* racemic form)**.

(Id. at claim 3 (emphasis added.)

136. In further support of the above discussion, several patents arising out of the Bayever patent family, including U.S. Patent Nos. 9,364,473 and 9,492,442,

contain method of treatment claims that are not limited to second-line therapy for pancreatic cancer. Even if Bayever was so limited, contrary to my opinion, it was not uncommon to consider or test a treatment on both first-line and second-line treatments. Patent Owner even acknowledges this during the prosecution of the '552 Patent with respect to the Alcindor reference. Specifically, Patent Owner noted that Alcindor was a review article summarizing the "Mathe Study." (Ex. 1084 at 381-82.) While most of the patients had undergone prior therapy, i.e., the treatment was being administered as a second-line therapy, Patent Owner acknowledged that 2 of the 23 participants (8.6%) had not undergone prior therapy and were therefore being given the treatment as a first-line therapy. (Id. at 382.)

137. In view of these teachings, a POSA would have immediately envisaged that the disclosed methods of Bayever could be considered for use in first-line treatment settings. A POSA would have understood Bayever was not intended to be limited to only second-line treatments.

E. Saif (Ex. 1007)

138. Saif, entitled "MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastasis Pancreatic Cancer," was authored by Dr. Muhammad Wasir Saif of Tufts University School of Medicine, and published online in the Journal of the Pancreas on May 2014 (Ex.

1007). I understand that Saif is prior art at least because it was a printed publication before the earliest possible claimed priority date of the ’815 Application.

139. Saif reviewed the results of a randomized large phase 3 clinical trial (the NAPOLI-1 study) using MM-398 (irinotecan liposome injection; also known as “nal-IRI”) conducted by Merrimack Pharmaceuticals, Inc. (Cambridge, MA, USA), in patients with metastatic pancreatic cancer who had previously received gemcitabine-based therapy. (Ex. 1007 at 1.) Saif summarized that the combination of MM-398 liposomal irinotecan with LV and 5-FU achieved its primary endpoint in a phase 3 trial and “achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2-month survival demonstrated by the control arm of 5-FU and leucovorin alone.” (Id.) Saif also states that, “a statistically significant advantage for progression free survival was also observed in the combination arm.” (Id.)

140. Saif found the results of the study to be “exciting, as currently FDA has approved no regimen for second-line treatment of pancreatic cancer” and “groundbreaking…in the gemcitabine-refractory setting.” (Id.)

141. Importantly, Saif specifically notes that because of these encouraging results of using MM-398 in second-line therapy, MM-398 should be further studied for potential use in first-line therapy in the FOLFIRINOX regimen. For example, Saif states:

> 2. Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment. [internal footnotes omitted].
>
> 3. **It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398**. However, bone marrow toxicity has to be borne in mind.

(Id.) A POSA would have understood this suggestion for further testing and replacing the non-liposomal irinotecan in FOLFIRINOX with a liposomal irinotecan, e.g., MM-398, to be a suggestion for a new or modified first-line therapy.

F. Ko (Ex. 1008)

142. Ko et al., entitled "A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer," was published online in the British Journal of Cancer on July 23, 2013 (Ex. 1008).

143. Ko, like other prior art references, evaluated liposomal irinotecan MM-398 (aka PEP02) as a treatment for pancreatic cancer. (Ex. 1008 at 1.) Ko administered MM-398 at a dose of 120 mg/m^2 that was diluted in 500 ml of 5% dextrose and delivered as a 90-min intravenous infusion every three weeks as a monotherapy for patients with metastatic pancreatic cancer. (Id. at 1-2.) Ko disclosed that dose adjustments were made according to toxicities, which included

decreasing the dose of PEP02 to 80 mg/m^2. (Id.) Ko further disclosed the use of premedications, including dexamethasone and a serotonin antagonist. (Id.)

144. Like other references discussed herein, Ko found that the liposomal irinotecan formulation may reduce toxicity while increasing efficacy of antitumor activity when compared to free irinotecan. (Id. at 5.)

145. Ko reports that the results of the phase II study met its primary endpoint of 75% of the 40 enrolled patients achieving a 3-month survival rate, with median progression-free survival and overall survival of 2.4 and 5.2 months, respectively. (Id. at 1.)

146. Ko states that, "[t]he results of this clinical trial are encouraging enough to warrant moving ahead with a larger study." (Id. at 5.) Notably, these suggestions are taken to heart by those in the field as Saif, published a year later, conducted the NAPOLI-1 phase III trial. Similar to Saif, Ko concludes that MM-398 should be further explored in the first-line therapy setting, by stating:

> 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 [MM-398] in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

(Id. (emphasis added).) A POSA would have understood this to be a suggestion to use or study liposomal irinotecan in first-line treatments.

G. Conroy 2013 (Ex. 1041)

147. Conroy et al., entitled "The Role of the FOLFIRINOX Regimen for Advanced Pancreatic Cancer," was published in Current Oncology Reports on January 23, 2013 (herein "Conroy 2013" (Ex. 1041)). I understand that Conroy 2013 is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

148. Conroy 2013 describes the "development of FOLFIRINOX Regimen." (Ex. 1041 at 2; see also id. at 1 (stating that the FOLFIRINOX regiment emerged in 2010).) Conroy 2013 discusses how FOLFIRINOX was developed, at least in part, because of the "synergism between oxaliplatin and 5-FU and between irinotecan and 5-FU" that led to regimens like FOLFOX and FOLFIRI and because "oxaliplatin and SN-38, the main active metabolite of irinotecan, showed synergistic activity in vitro." (Id. at 2.)

149. The "promising activity" of the FOLFIRINOX regimen prompted further studies, including Conroy, which is discussed and summarized in Conroy 2013. (See id. at 182-187.) However, Conroy 2013 acknowledges that even in 2010 there were "doubts" and "concerns" raised "regarding safety" and "differing toxicity profiles of FOLFIRINOX. (Id. at 1, 4.) As a result, FOLFIRINOX regimens were modified. (Id. at 4.) In fact, in one study, the regimen was modified in 50.8% of patients "because of concern for potential toxicities." (Id. (stating "deletion of bolus

5-FU and dose reduction of irinotecan were the commonest modifications").) Conroy 2013 discloses other studies from Emery, Memorial Sloan-Kettering Cancer Center, Yale (and other well-respected institutions) where patients were treated with modified regimens of FOLFIRINOX that included (1) deleting the bolus, (2) deleting the bolus and administering prophylactic pegfilgrastim, (3) and substantial dose reductions: with median relative doses of 57-100%. (Id. at 4-5.) Conroy 2013 further notes that despite these modifications, efficacy was maintained, response rates remained promising, and/or that patients achieved disease control. (Id.)

150. Conroy 2013 also disclosed that "other modifications of FOLFIRINOX have been proposed." (See id. at 5 (identifying some such proposals).)

151. In conclusion, Conroy states that FOLFIRINOX is now the reference treatment in patients with good performance status and is cost-effective" but that "further investigation is needed to continue improving survival outcomes in these patients with identification of predictive biomarkers and to develop further combination or maintenance therapeutic strategies." (Id. at 6.)

H. Masi (Ex. 1012)

152. Masi et al., entitled "First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule," was published in the Annals of Oncology in 2004 (Ex. 1012). I understand that Masi is prior art at least because

it was a printed publication before the earliest possible claimed priority date of the '815 Application.

153. Masi noted that not all patients who receive first-line treatments are able to receive second-line treatments. (Ex. 1012 at 2.) Clinical trial data suggests that "approximately 20% to 40% of patients, mainly because of deterioration of their performance status and liver function, will not be fit enough to undergo further chemotherapy [after a first-line treatment] and will receive only supportive care." (Id.) It also noted that exposure of metastatic cancer to the three most active agents, "5-FU/LV, irinotecan, and oxaliplatin, is associated with promising survival" and therefore suggested that "if feasible and tolerable, the best way to expose 100% of patients to all these three active agents might be to administer them upfront." (Id.) A POSA would understand that Masi was suggesting that a second-line treatment should be considered as a first-line therapy option.

154. Masi therefore evaluated a simplified FOLFOXIRI regimen of irinotecan, oxaliplatin, leucovorin, and 5-FU that could be less myelotoxic and more easily administered in clinical practice for the first-line treatment of metastatic colorectal cancer. (Id. 1-2.) This modified regimen includes a biweekly administration, with slightly reduced doses of irinotecan and oxaliplatin and a continuous infusion (rather than a chronomodulated infusion) of 5-FU. (Id.)

155. Masi notes that "experimental studies have shown a synergic or additive interaction between SN-38 (the active metabolite of irinotecan), oxaliplatin, and 5-FU" and "these agents have different mechanisms of action and dose-limiting toxic effects." (Id. at 1.) Masi therefore adopted an administration sequence of irinotecan before oxaliplatin followed by 5-FU because "*in vitro* studies on two human colon cancer cell lines showed that synergy occurs only when irinotecan precedes oxaliplatin and 5-FU exposure." (Id. at 5.) Masi indicates that a biweekly schedule was chosen because this schedule had demonstrated a favorable toxicity profile in previous studies, which allows the delivery of significant dose intensities, and is active and convenient in an outpatient setting. (Id.) Masi further states that 5-FU was administered as a continuous infusion without any bolus to reduce the related toxic effects, thus favoring its combination with optimal doses of irinotecan and oxaliplatin." (Id.)

156. Masi concludes that this simplified FOLFOXIRI regimen showed an improved safety profile while maintaining antitumor activity and efficacy. (Id. at 6.) A POSA would appreciate that such regimens should be considered for first-line therapy of metastatic colorectal cancer and perhaps other tumors.

I. Ginocchi (Ex. 1016)

157. Ginocchi et al., entitled "Modified FOLFOXIRI In Advanced Pancreatic Cancer," was published in the Annals of Oncology in September 2012

(Ex. 1016). I understand that Ginocchi is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

158. Ginocchi notes the toxicity concerns known with the FOLFIRINOX treatment and describes a modified FOLFOXIRI regimen administered to metastatic and local advanced cancer patients, where the doses of irinotecan and 5-FU were lowered. (Ex. 1016 at 1.) Of the 39 patients treated, no toxic deaths or febrile neutropenia were reported, and median progression-free survival was 11.5 months, and median overall survival was 25.5 months. (Id.) The authors concluded that this modified FOLFOXIRI regimen was "quite well tolerated and it maintained its good activity in metastatic pancreatic cancer." (Id.)

J. Carnevale (Ex. 1013)

159. Carnevale et al., entitled "MM-398 (Nanoliposomal Irinotecan): Emergence of a Novel Therapy for the Treatment of Advanced Pancreatic Cancer," was published online in Future Oncology on December 21, 2015 (Ex. 1013). I understand Carnevale is prior art at least because it is a printed publication before this effective filing date if the effective filing date of the '552 patent is deemed to be no earlier than November 10, 2017.

160. Carnevale reviews then recent developments of administering liposomal irinotecan MM-398 in the clinical setting. After discussing MM-398's improved safety, toxicity, and pharmacokinetic properties over standard irinotecan

and its FDA approval under the name Onivyde for use in combination with 5-FU and leucovorin for second-line treatment of pancreatic cancer patients, Carnevale concludes that:

> 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 extension*** of MM-398's role in metastatic pancreatic cancer.

(Ex. 1013 at 11 (emphasis added).)

K. Dean (Ex. 1014)

161. Dean et al., entitled "A randomized, open-label phase II study of nanoliposomal irinotecan (nal-IRI)-containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated metastatic pancreatic adenocarcinoma (mPAC)," was published in a supplement to the Journal of Clinical Oncology on February 1, 2016 (Ex. 1014). I understand Dean is prior art if the effective filing date of the '552 patent is deemed to be no earlier than November 10, 2017.

162. Dean is an abstract that reports an open-label phase 2 trial to determine the efficacy and safety of liposomal irinotecan MM-398 with 5-FU, leucovorin, and oxaliplatin in first-line therapy of pancreatic cancer patients. (Ex. 1014 at 2-3.) Dean notes that FOLFIRINOX had emerged as the standard of care for first-line treatment

of metastatic pancreatic cancer. Dean also discloses the FDA clinical trial protocol number NCT02551991. (Id. at 3.)

L. Additional Prior Art and References

163. In addition to the references discussed above and throughout this declaration, I utilize the knowledge and expertise of a POSA. Also, in this declaration I cite to references in addition to those recited and summarized above, including to provide background on the state of the art at the date. All references, whether summarized above or not, that were publicly available prior to the priority date of the '552 patent, are within the scope of the prior art.

M. Rebuttal of Patentee Arguments Regarding Unexpected Results During Patent Prosecution

164. As noted above, I reviewed the file history. In response to a rejection, the alleged inventors argued that there were unexpected results for the claimed regimen. I understand that the legal requirement for unexpected results is a difference in kind (rather than simply a difference in degree), and that the results would have been unexpected to a POSA. In my opinion, there is not only no difference in kind, but no difference in degree. Furthermore, since the prior art suggested that the claimed formulation was superior to unencapsulated irinotecan, a POSA would have expected the claimed regimen to be superior to the prior art FOLFIRINOX regimen, as that was the POSA's motivation for developing the claimed regimen. I also understand that an inquiry regarding unexpected results is

not limited to prior art, or even art available at the time of patent allowance but is an objective inquiry of all available evidence. Thus, I have reviewed recent literature on this topic, which supports my opinion that the patentees' assertion during patent prosecution is not supported by the totality of the evidence. Two recent review articles are consistent with my opinion.

a. Nichetti (Ex. 1010)

165. Nichetti et al., entitled "NALIRIFOX, FOLFIRINOX, and Gemcitabine with Nab-Paclitaxel as First-Line Chemotherapy for Metastatic Pancreatic Cancer: A Systemic Review and Meta-Analysis," was published in JAMA Network Open on January 8, 2024 (Ex. 1010).

166. Nichetti evaluated data from phase 3 clinical trials that investigated NALIRIFOX (which is an embodiment of the claims of the '552 patent and is a four-drug combination of liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin), FOLFIRINOX (a prior art regimen, which is a four-drug combination of irinotecan, oxaliplatin, 5-FU, and leucovorin), and GEM-NABP (a combination of gemcitabine and nab-paclitaxel) as first-line treatment of metastatic pancreatic cancer to compare their reported overall survival (OS) and progression-free survival (PFS). (Ex. 1010 at 1.)

167. Nichetti reported that there was "**no difference observed**" in overall survival between NALIRIFOX (11.1 months) and FOLFIRINOX (11.7 months),

and "[a]nalysis of 6- and 12-month OS did not find statistically significantly higher OS for NALIRIFOX compared with FOLFIRINOX." (Id. at 1, 5.) Nichetti further states:

> Furthermore, ***there was no significant difference*** in OS among patients treated with NALIRIFOX compared with those treated with FOLFIRINOX. Indeed, NALIRIFOX failed to break the symbolic wall of 12 months of median OS, thus questioning the real improvement shown in the NAPOLI 3 trial. This result is even more relevant considering that NALIRIFOX and FOLFIRINOX are similar in terms of type and dosage of the drugs administered, ***but with an unfavorable cost-effectiveness ratio***. In fact, the mean cost per cycle of liposomal irinotecan has been estimated ***as more than 100-fold that of irinotecan.***

(Id. at 9 (emphasis added).)

168. Nichetti concludes that its "data do not suggest a preference between NALIRIFOX and FOLFIRINOX, which can thus be still considered a valid option to be further explored in its modified version in the metastatic disease setting." (Id. at 10.)

b. Nevala-Plagemann (Ex. 1011)

169. Nevala-Plagemann et al., entitled "NALIRIFOX for metastatic pancreatic adenocarcinoma: hope or hype," was published in Nature Reviews Clinical Oncology in August 2024 (Ex. 1011).

170. Nevala-Plagemann states that in comparison with the PRODIGE 4 (containing a FOLFIRINOX arm), "NALIRIFOX does not seem to raise the bar, but

rather exposes patients and health-care systems to financial toxicities," and "A recently published systematic review and meta-analysis supports our conclusion that the differences in OS between NALIRIFOX and modified FOLFIRINOX are **not clinically significant** and that those in neuropathy are **not statistically significant**." (Ex. 1011 at 1-2 (emphases added).) More specifically, Nevala-Plagemann reports that the "median OS [overall survivability] of patients receiving NALIRIFOX in NAPOLI 3 is **identical** to that of those who received FOLFIRINOX in PRODIGE 4 (11.1 months)." (Id. at 1 (emphasis added).) With regard to toxicity, Nevala-Plagemann further states, "6.5% of patients receiving NALIRIFOX had grade ≥3 peripheral neuropathy (3% peripheral neuropathy and 3.5% peripheral sensory neuropathy) compared to 9% of patients receiving FOLFIRINOX in PRODIGE 4, **a clinically insignificant difference**." (Id. at 2 (emphasis added).) The results are summarized in Table 1 (reproduced below).

Table 1 | Key features of NALIRIFOX versus FOLFIRINOX

Regimen and trial	Baseline patient characteristics			Efficacy outcomes			Grade ≥3 AEs			Cost per single 2-week cycle[a]
	Median age	Serum albumin levels (inclusion criteria)	Prior chemotherapy	mOS	mPFS	ORR	Diarrhoea	Neutropenia and febrile neutropenia	Neuropathy	
NALIRIFOX (NAPOLI 3)[3,9]	64 years	≥3 g/dl	4% of patients	11.1 months	7.4 months	41.8%[b]	20%	24% and 2%[c]	6.5%[d]	US $7,800
FOLFIRINOX (PRODIGE 4)[1]	61 years	No restriction	Not allowed	11.1 months	6.4 months	31.6%	13%	46% and 5%	9%	$500

[a]Approximate average wholesale cost for nanoliposomal irinotecan or irinotecan for a patient with a body surface area of 2.0 m^2. [b]No central review of images. [c]Primary prophylaxis with granulocyte colony-stimulating factor was encouraged in NAPOLI 3 and not recommended in PRODIGE 4. [d]Includes peripheral neuropathy and peripheral sensory neuropathy[3]. AE, adverse event; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; mOS, median overall survival; mPFS, median progression-free survival; NALIRIFOX, nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin; ORR, objective response rate.

IX. OVERVIEW OF THE ’552 PATENT

A. The Specification and Claims of the ’552 Patent

171. I have read the ’552 Patent, titled “Methods for treating metastatic pancreatic cancer using combination therapies comprising liposomal irinotecan and oxaliplatin,” and reviewed the relevant portions of the prosecution history of the ’552 patent. The ’552 patent issued from U.S. Non-Provisional Patent Application No. 15/809,815 (“the ’815 Application”), filed on November 10, 2017, which is a continuation of U.S. Non-Provisional Patent Application No. 15/241,106, filed August 19, 2016 (“the ’106 Application”), which claims the benefit of priority to U.S. Provisional Application No. 62/208,209 filed August 21, 2015 (“the ’209 Provisional”), U.S. Provisional Application No. 62/216,736 filed September 10, 2015 (“the ’736 Provisional”), U.S. Provisional Application No. 62/273,244 filed December 30, 2015 (“the ’244 Provisional”), U.S. Provisional Application No. 62/281,473 filed January 21, 2016 (“the ’473 Provisional”), U.S. Provisional Application No. 62/302,341 filed March 2, 2016 (“the ’341 Provisional”), U.S. Provisional Application No. 62/323,245 filed April 15, 2016 (“the ’245 Provisional”), and U.S. Provisional Application No. 62/343,313 filed May 31. 2016 (“the ’313 Provisional”). (Ex.1001 at 1:9-17.) The entire contents of which are incorporated herein by reference. The ’552 patent lists Eliel Bayever, Sarah F.

Blanchette, Jonathan Basil Fitzgerald, Daniel F. Gaddy, Bart S. Hendriks, Ashish Kalra, and Helen Lee as the inventors and Ipsen Biopharm Ltd as the Assignee.

172. The background of the '552 patent recognizes that tolerability of multi-drug regimens is important in cancer treatment. (Ex. 1001 at 1:47-2:6.) The '552 patent acknowledges the FOLFIRINOX regimen (5-fluorouracil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin) was a standard of care for first-line treatment of metastatic pancreatic cancer, and that FOLFIRINOX had been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011, although there were some concerns about its toxicity. (Id. at 1:47-67.) The '552 patent also states that due to toxicity, modified FOLFIRINOX regimens are often used (e.g., elimination of the 5-FU bolus). (Id. at 2:3-6.)

173. The '552 patent states that,

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

(Id. at 2:47-57.)

174. The ’552 patent describes the liposomal irinotecan as irinotecan sucrose sulfate liposome injection (otherwise termed “irinotecan sucrose octasulfate salt liposome injection” or “irinotecan sucrosofate liposome injection”). (Id. at 10:66-11:9.) The ’552 patent states that “the formulation referred to herein as ‘MM-398’ (also known as PEP02, see U.S. Pat. No. 8,147,867) is a form of ‘nanoliposomal irinotecan’ (also called ‘irinotecan liposome’ or ‘liposomal Irinotecan’), and “MM-398 is the irinotecan sucrose octasulfate salt encapsulated in a nanoliposome drug delivery system.” (Id. at 11:4-9.)

175. Example 1 of the ’552 patent describes tumor exposure of SN-38 in patients administered free irinotecan or MM-398, and Example 2 describes evaluation of *in vivo* tolerability and efficacy of combination therapies in an animal model. (Id. at 19:68-21:28.) Example 3 contains a study protocol—but not data—to compare the following regimens: (1) MM-398+5-FU/LV+oxaliplatin (Arm 1), (2) MM-398+5-FU/LV (Arm 2), and (3) nab-paclitaxel+gemcitabine (Arm 3). (Id. at 21:32-40.) The ’552 patent states that, “MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen, and “The addition of oxaliplatin to the NAPOLI-I regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398’s superior PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the

efficacy of FOLFIRINOX).” (Id. at 21:50-56.) Example 4 describes the results of a phase 1 trial of a treatment regimen combining liposomal irinotecan, 5-FU/LV, and oxaliplatin. While the Example clearly describes administration of three different dosing regimens to patients with previously untreated pancreatic cancer, it does not describe any therapeutic benefit (clinical efficacy) in any patients. Example 5 is a description of ONIVYDE® (Irinotecan Liposome Injection) Liposomal Irinotecan. (Id. at 43: 21-46:61.) None of these examples suggests to a POSA that the inventors recognized that they possessed a method of treating metastatic pancreatic cancer patients with any therapeutic benefit (clinical efficacy).

176. The ’552 patent has two independent claims (claims 1 and 12) and thirteen dependent claims (claims 2-11 and 13-15).

177. Independent claim 1 recites:

> 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 (1)-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.

178. Claim 2 depends from claim 1 and recites, "each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan."

179. Claim 3 depends from claim 1 and recites, "the 5-fluorouracil is administered as an infusion over 46 hours."

180. Claim 4 depends from claim 1 and recites, "the leucovorin is administered immediately prior to the 5-fluorouracil."

181. Claim 5 depends from claim 1 and recites, "the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle."

182. Claim 6 depends from claim 1 and recites, "the liposomal irinotecan is administered as an infusion over about 90 minutes."

183. Claim 7 depends from claim 1 and recites, "the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil."

184. Claim 8 depends from claim 1 and recites, "the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes."

185. Claim 9 depends from claim 1 and recites, "the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-

glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxy polyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE)."

186. Claim 10 depends from claim 1 and recites, "the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonyl methoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanol amine (MPEG-2000-DSPE)."

187. Claim 11 depends from claim 10 and recites, "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.

188. Independent claim 12 recites:

> 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 (1)-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.

189. Claim 13 depends from claim 1 and recites, "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.

190. Claim 14 depends from claim 12 and recites, "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."

191. Claim 15 depends from claim 1 and recites, "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."

B. The Prosecution History of the '552 Patent

192. The '815 Application that issued as the '552 patent was filed on November 10, 2017. The application had 20 claims including independent claims 1, 16, and 19. Claim 1 recited:

> A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
> a. 60 mg/m^2 of liposomal irinotecan,
> b. 60 or 85 mg/m^2 oxaliplatin,
> c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
> d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

(Ex. 1084 at 60.)

193. Claim 16 recited:

> A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
> a. 60 mg/m^2 of liposomal irinotecan,
> b. 85 mg/m^2 oxaliplatin,

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

(Id. at 61.)

194. Claim 19 recited:

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

(Id. at 63.)

195. On March 6, 2018, the Patent Office issued a Non-final Office Action, rejecting the claims for, among other rejections, obviousness. (Ex.1084 at 192.) Claims 1-3, 5-8, 10, 16 and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever et al. (WO 2013/188586) ("Bayever"), in view of Conroy et al. (N Engl J Med. 2011 May 12;364(19):1817-25) ("Conroy"). (Id.) Claims 4, 9, and 18 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Fleming et al. (https://www.oncologynurseadvisor.com/features/importance-of-sequence-in-

chemotherapy-administration/) ("Fleming"). (Id. at 194-195.) Claims 11-15, 17, and 20 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy as evidenced by Bayever et al. (WO 2016/094402) ("Bayever II"). (Id.) Claims 1-20 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U S. Patent No. 9,492,442 ("'442 patent") in view of Conroy. (Id. at 196.)

196. In its response dated August 6, 2018, the Applicant made the following amendments to independent claim 1:

> 1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
> a. 60 mg/m^2 of liposomal irinotecan,
> b. 60 ~~or 85~~ mg/m^2 oxaliplatin,
> c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
> d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

(Id. at 287.)

197. The Applicant also canceled claims 2, 3, 16, 17, and 20 and added new claims 21 and 22. (Id. at 291.)

198. On September 11, 2018, the Patent Office issued a Final Office Action, rejecting the claims for, among other rejections, obviousness. (Id. at 314-27.)

Claims 1-3, 5-8, 10, and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Alcindor et al. (Curr Oncol. 2011 Jan;18(1):18-25) ("Ex. 1027"). (Id. at 316.) Claims 1, 4-15, 18-19, and 21-22 were rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of the '442 patent, in view of Conroy and further in view of Alcindor. (Id. at 323.)

199. While the Applicant indicated in its response dated February 11, 2019 that independent claims 1 and 19 have been amended to "even more clearly recite the subject matter being claimed," the only amendments were directed to punctuation and changing, in dependent Claim 11, the phrase "liposome vesicles consisting of" to "liposomes composed of." (Id. at 393).

200. On July 8, 2019, the Patent Office issued a Non-Final Office Action, rejecting the claims for, among other rejections, obviousness. (Ex. 1088 at 59.) Claims 1-3, 5-8, 10, and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Melis et al. (The Society for Surgery of the Alimentary Tract; 52nd Annual Meeting Posters, May 6 - 10, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) ("Melis"). (Id.) Claims 4, 9, 18, and 23 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Melis and further in view of Fleming. (*Id.*, 62.) Claims 11-15 and 21-22 were rejected under

35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Melis and as evidenced by Bayever II. (*Id.*, 64.) 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 the '442 patent, in view of Conroy and further in view of Melis. (*Id.*, 65.)

201. In its response dated January 7, 2020, the Applicant made a minor amendment to independent claims 1 and 19 to recite "200 mg/m^2 of the (*l*) form of leucovorin or 400 mg/m^2 of the (*l*+*d*) racemic form of leucovorin." (Ex. 1091 at 350-352.)

202. In the Final Office Action dated February 27, 2020, the Patent Office maintained the rejections against claims 1, 5-8, 10, and 19 under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Melis. (Ex. 1097 at 190-195.) The Patent Office also maintained the rejections against claims 4, 9, 18, and 23 under 35 U.S.C. § 103 as being unpatentable over Bayever, Conroy, in view of Melis and further in view of Fleming. (Id. at 195-197.) The Patent Office further maintained the rejections against claims 11-15 and 21-22 under 35 U.S.C. § 103 as being unpatentable over Bayever, Conroy, in view of Melis and as evidenced by Bayever II. (Id. at 197-199.) Finally, the Patent Office maintained the rejections against claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory

double patenting as being unpatentable over claims 1-18 of the ’442 patent, in view of Conroy and further in view of Melis. (Id. at 200-201.)

203. In its response dated January 7, 2020, the Applicant made the following amendments to independent claims 1 and 19:

> 1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~: a 60 mg/m^2 of liposomal irinotecan.
> b.60 mg/m^2 oxaliplatin,
> c.200 mg/m^2 of 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.
>
> 19. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~:
>
> a. 60 mg/m^2 of liposomal irinotecan,
> b. 60 mg/m^2 oxaliplatin,
> c. 200 mg/m^2 of 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.

(Ex. 1098 at 212-214.)

204. On August 26, 2021, the Patent Office issued a Non-final Office Action, rejecting the claims for, among other rejections, obviousness. (Ex. 1119 at 11-18.) The Patent Office once again maintained the same rejections against claims 1, 5-8, 10, and 19 under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Melis, against claims 4, 9, 18, and 23 under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Fleming, against claims 11-15 and 21-22 under 35 U.S.C. § 103 as being unpatentable over Bayever, Conroy, in view of Melis and as evidenced by Bayever II. (Id.) Finally, the Patent Office also maintained the rejections against claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of the '442 patent, in view of Conroy and further in view of Melis. (Id. at 19).

205. In its response dated February 25, 2022, the Applicant did not make any further amendments to the claims. (Ex. 1119 at 140-42.) Instead, Applicant argued that there was (1) no motivation to combine the references (2) no reasonable expectation of success, and (3) unexpected results. (Id.)

206. First, Patent Owner admitted, throughout prosecution, that Bayever discloses a treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2), in combination with LV (e.g., 400 mg/m^2 *l+d* form) and 5-FU (e.g., 2,400 mg/m^2) to a patient once every two weeks.

(See Ex. 1084 at 292.) Patent Owner also repeatedly admitted that Conroy discloses administering to patients with first-line metastatic pancreatic cancer, a combination of 85 mg/m^2 of oxaliplatin, 180 mg/m^2 non-liposomal irinotecan, 400 mg/m^2 LV, 400 mg/m^2 5-FU as bolus injection followed by 2,400 mg/m^2 5-FU as a continuous infusion once every two weeks. (See id. at 292, 381.)

207. Patent Owner argued, however, that there was no motivation to combine these references (with each other or other references). Patent Owner's first argument was that neither Bayever nor Conroy taught co-administration of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin. (Ex. 1119 at 145.) Differences between Conroy and Claim 1 as articulated by Patent Owner are reproduced below but with an inclusion of Bayever's admitted disclosures:

Bayever	Conroy	Claim 1 of the '552 Patent
60 mg/m^2 liposomal irinotecan 0 mg/m^2 oxaliplatin; 400 mg/m^2 leucovorin; 2400 mg/m^2 5-FU	180 mg/m^2 non-liposomal irinotecan; 85 mg/m^2 oxaliplatin; 400 mg/m^2 leucovorin 2800 mg/m^2 5-FU	60 mg/m^2 liposomal irinotecan; 60 mg/m^2 oxaliplatin; 400 mg/m^2 leucovorin 2400 mg/m^2 5-FU

208. Patent Owner focused on the references individually—instead of what was more broadly known or understood by the POSA—to argue there is "no mention of any liposomal irinotecan ***in Conroy*** or adjusting any of the dosages ***in Conroy***" to arrive at the claimed subject matter. (Id. (emphasis added).) Similarly, Patent Owner argued that "nowhere does Bayever teach or suggest incorporating

oxaliplatin into its therapeutic regimen." (Id.) Patent Owner further argued there was also no basis to combine because there is "no basis to combining teachings regarding second-line therapy with teachings regarding first-line therapy" and claimed Bayever's teachings are only for second-line treatment and Conroy's are only for first-line treatment. (Id. at 146.)

209. Despite admitting that Melis discloses the use of 60 mg/m^2 of oxaliplatin in the treatment of advanced pancreatic cancer and acknowledging that Conroy discloses the use of oxaliplatin (at a higher dose) with irinotecan, leucovorin, and 5-FU, Patent Owner argued there is no evidence that it was obvious to try using 60 mg/m^2, and thus combine the art, because ***Melis*** did not disclose such use with irinotecan or leucovorin and ***Melis*** did not recognize predictable outcomes of coadministration, e.g., tolerability or efficacy. (Id. at 146-147.) That is, Patent Owner again focused on each reference in isolation and ignored the teachings of other art known to a POSA, e.g., Patent Owner ignored that Conroy's disclosure of a dose of oxaliplatin of at least 60 mg/m^2 showed such tolerability.

210. Second, Patent Owner argued a POSA had no reasonable expectation of success in combining the references. Patent Owner argued that a POSA could not expect "a reasonable expectation of similar results" in combining teachings of first- and second-line treatments and because there was no comparison of liposomal vs. non-liposomal irinotecan. (Id. at 148-49.) Patent Owner argued a POSA would not

have been motivated to use a different (lower) dose of oxaliplatin and argued that such a combination was not tolerable, but the only alleged support for this comes from a post-filing paper. (Id. at 149-50.)

211. Finally, Patent Owner argued that the claimed subject matter produced unexpected results. Patent Owner relies on a 2020 paper to argue that of different dosages, only the claimed dosage was purportedly tolerable and had efficacy outcomes higher than FOLFORINX. (Id. at 152-53.) In relying on the post filing Wainberg references (Wainberg Z, et al., Ann Oncol. 3l (Suppl 3):S241 (2020) ("Wainberg abstract"); corresponding poster ("Wainberg poster") and presentation ("Wainberg presentation")) (Ex 1018) purported to show unexpected results, Patent Owner argued that Wainberg showed that the claimed dose of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin (60/60) was more tolerable than regimens with higher doses of either liposomal irinotecan or oxaliplatin. (Ex. 1119 at 153; Ex. 1018.)

212. On April 11, 2022, the Patent Office issued a Notice of Allowance without stating specific reasons for allowance, and indicated that claims 1, 4-13, 19, and 21-23 were allowed, and claims 14, 15, and 18 were canceled. (Ex.1123 at 461-63.)

213. During prosecution, it is my understanding that Patent Owner submitted over 1,000 references in a total of thirty-six Information Disclosure Statements

("IDSs"): submitting an IDS on August 6, 2018, three on February 11, 2019, four on February 13, 2019, four on January 7, 2020, four on January 9, 2020, seven on February 25, 2021, six on March 12, 2021, one on May 26, 2021, one on March 9, 2022, four on March 10, 2022, and one on March 11, 2022. Mahaseth, Ko, Cantore, and Dean were disclosed as part of 242 total disclosures identified by the Patent Owner between February 11-13, 2019. Conroy 2013, Saif, Masi, Ginocchi, and Carnevale were not disclosed or considered during prosecution. (Of course, Nichetti and Nevala-Plagemann had not yet been published.)

C. The Priority Date of the '552 Patent

214. I understand that the cover of the '552 patent lists the seven provisional applications and one non-provisional application, the '106 Application, under the heading "related U.S. Application Data," to which the '552 patent claims priority. (See Section VI(A).) I further understand that these were the applications filed prior to the non-provisional '815 application, from which the '552 patent was issued.

215. I am told that to establish priority, the earlier application must describe the later-claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought—which I understand to mean that the earlier disclosure must describe and enable the later-claimed invention with all of its limitations. I further understand that

a plan to obtain or achieve the claimed invention in the future is insufficient to show possession at the time of filing.

216. In the event that the "method of treatment" term is construed to require efficacy in actually alleviating the progression of pancreatic cancer in humans, it is my opinion that the claims of the '552 patent cannot find support for this claim limitation in any application to which a prior claim of priority is made. Because, as explained below, the prior applications to which the '552 patent claim priority do not provide sufficient detail to show a POSA that the claimed subject matter actually provided any benefit to patients with pancreatic cancer, it is my opinion that the earliest potential priority claim would be limited to the filing date of the '815 Application, which was November 10, 2017.

217. Neither the multiple provisional applications nor the '106 Application, to which the '552 patent claims priority, describe data showing efficacy of the claimed regimen in a human study. Indeed, all the provisional applications and the '106 Application only contain a phase 2 study protocol to assess, in the future, the preliminary efficacy and safety of the Nal-IRI (also referred to as MM-398), oxaliplatin, LV, and 5-FU regimen. (See, e.g., Ex. 1015 at Example 1; Ex. 1028 at Example 1; Ex. 1029 at Example 1; Ex. 1030 at Example 1; Ex. 1031 at Example 1; Ex. 1032 at Example 1; Ex. 1060 at Example 1; Ex. 1020 at Example 3.)

218. Specifically, the ’209 Provisional notes that two combination chemotherapy regimens—FOLFIRINOX and nab-paclitaxel + gemcitabine—had emerged as the standard of care options for first-line treatment of metastatic cancer, which had median overall survival rates of 11.1 and 8.5 months, respectively, according to separate phase 3 studies. (Ex. 1015 at ¶ [00112].) It then noted that patients with metastatic pancreatic cancer who had received and progressed on gemcitabine, a combination of 5-FU/LV with nal-IRI (which is “also known as MM-398” and which is “a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation”) demonstrated “significant clinical activity, increasing OS and PFS relative to 5-FU/LV.” (Id.) As a result, the ’209 Provisional proposed a study: “***The goal of this current study*** is to assess the preliminary efficacy and safety of nal-IRI-containing regimens.” (Id. (emphasis added); see also id at ¶ [00204])

219. Specifically, the ’209 Provisional proposed a “***study to assess the preliminary efficacy and safety***” of the following “in previously untreated metastatic pancreatic cancer patients ***to assess the most promising regimen for further development***:” (1) “***nal-IRI + 5-FU/LV + oxaliplatin***” and (2) “nal-IRI + 5-FU/LV.” (Id. at ¶ [00112] (emphasis added).) These two regimens were to be compared to nab-paclitaxel + gemcitabine. (Id. at ¶ [00122].) The regimens were as follows:

i. nal-IRI + 5-FU/LV + oxaliplatin (Arm 1)

ii. nal-IRI + 5-FU/LV (Arm 2)

iii. nab-paclitaxel + gemcitabine (Arm 3)

(Id.)

220. The stated "primary objectives" were to "evaluate the safety and tolerability of [Arm 1]" and "characterize dose-limiting toxicities (DLTs) associated with [Arm 1] and determine the Part 2 dose of the triplet combination." (Id. at ¶ [00114]; see also id. at ¶ [00122].) The primary objectives further included "assess[ing] the efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to Arm 3." (Id. at ¶ [00115].) The "secondary objectives" were to "characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin." (Id. at ¶¶ [00116]-[00117].) The study also sought to "assess efficacy of each nal-IRI containing regimen relative to [Arm 3]" and to (i) "assess tumor CA19-9 response" in each Arm (ii) "assess health-related quality of life" in each Arm, and (iii) "compare the safety and adverse event profile" between the Arms. (Id. at ¶¶ [00118], [00122])

221. Additional details about how the study would be conducted, what would be considered, who would be excluded, how long the study would last, etc., were also identified. (See, e.g., id. at ¶¶ [00123]-[00145], [00165]-[00195].)

222. Importantly, Arm 1 is described as comprising nal-IRI (administered at 80 mg/m^2), then oxaliplatin (administered in doses ranging from 60-85 mg/m^2), then LV (l + d form, administered at 400 mg/m^2), and finally 5-FU (administered at 2400 mg/m^2). (Id. at ¶¶ [00146]-[00153].) The study design contemplated that the oxaliplatin dose would be reduced (from 85 mg/m^2 to 60 mg/m^2) for at least some patients, including to test for unexpected toxicities. (Id. at ¶ [00277].) The nal-IRI dose was also contemplated as being reduced (from 85 mg/m^2 to 60 mg/m^2) if, e.g., a patient was known to be homozygous for *UGT1A1*28*, present in approximately 10% of Caucasians. (Id. at ¶¶ [0061], [00264].) These reduced doses would also be administered upon agreement of the Investigators, the Sponsor, and the Medical Monitor. (Id. at ¶ [00288].)

223. The total enrollment for the study was estimated to be approximately 156-168 patients. (Id. at ¶ [00135].)

224. A similar future-looking phase 2 protocol is described in the other provisional applications and in the ’106 non-provisional application. (*See generally* Exs. 1020, 1038-1032.)

225. That is, a POSA would have understood from each of the seven provisional applications and from the ’106 Application that the Patent Owner had created a study protocol to test, at some point in the future, the efficacy, safety, and tolerability of a drug combination including nal-IRI or MM-398 (administered at 80

mg/m^2), then oxaliplatin (administered in doses ranging from 60-85 mg/m^2), then LV (l + d form, administered at 400 mg/m^2), and finally 5-FU (administered at 2400 mg/m^2, i.e., Arm 1. Therefore, a POSA would know that the Patent Owner had no real data, only hypotheses, as to what the efficacy, safety, or tolerability of such a treatment would be at the time it filed any one of these applications.

226. In addition, nowhere in any of the applications to which the '552 Patent claims priority is any suggestion that a patient had actually received the treatment claimed in the '552 Patent, i.e., a treatment of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 400 mg/m^2 LV l + d form (or 200 mg/m^2 (l)-form), and 2400 mg/m^2 5-FU. Therefore, not surprisingly, there are also no data about the actual efficacy, safety, or tolerability of the treatment.

227. Therefore, it is my opinion that a POSA would not recognize that the inventors of the '552 Patent had possession of the claimed invention based on any priority claim made. Therefore, it is my opinion that a POSA would recognize that the '552 Patent's priority claim, i.e., any possession of the claimed subject matter, cannot be made to anything earlier than November 10, 2017, which is the date the '815 Application was filed.

X. UNPATENTABILITY OF THE ’552 PATENT

228. As explained below, in my opinion, claims 1-15 of the ’552 patent would have been obvious over the references discussed below and general knowledge before the effective filing date of the ’552 patent.

A. GROUND 1: CLAIMS 1, 3-6, AND 8-14 WOULD HAVE BEEN OBVIOUS OVER CONROY, CONROY PROTOCOL, AND MAHASETH IN COMBINATION WITH THE SKILL AND KNOWLEDGE OF A POSA, INCLUDING BAYEVER, SAIF, KO, AND CANTORE; ANY ALLEGED UNEXPECTED RESULTS ARE CONTRADICTED BY NICHETTI AND NEVALA-PLAGEMANN

229. As discussed below, in my opinion, claims 1, 3-6, and 8-14 would have been obvious in view of the state of the art and a skilled artisan’s general knowledge before the effective filing date of the ’552 patent, in particular, Conroy, Conroy Protocol, and Mahaseth in combination with a POSA’s skill and knowledge. Moreover, the unexpected results alleged during patent prosecution are contradicted and ultimately refuted by the disclosures of Nichetti and Nevala-Plagemann.

230. The teachings of Bayever, Saif, Ko, Nichetti, and Nevala-Plagemann are detailed above in Section X.

a. Claim 1 would have been obvious over Conroy, Conroy Protocol and Mahaseth in combination with the knowledge and skill of a POSA, including Bayever, Saif, Ko, and Cantore and in further view of Nichetti and Nevala-Plagemann

231. Independent claim 1 recites:

> **Claim 1:** A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient 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 (1)-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.

232. In my opinion, claim 1 would have been obvious over the prior art at least because the claimed method of treatment involves administering an antineoplastic therapy consisting of liposomal irinotecan, oxaliplatin, and 5-fluorouracil – the same four-drug combination as in the established gold-standard FOLFIRINOX regimen for first-line treatment of metastatic pancreatic cancer.

233. The FOLFIRINOX regimen as first described by Conroy et al. consists of 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin, and 5-FU, first administered as a 400 mg/m^2 bolus and then 2400 mg/m^2 5-FU infusion, administered every two weeks in first-line therapy in patients with metastatic pancreatic cancer. (Ex. 1003 at 1.)

234. A POSA would have been motivated to modify this regimen for several reasons. Modifications to reduce toxicity were widely practiced, such as reducing the doses of the multiple drugs in the regimen. (See, e.g., Section VII.D.)

235. First, a POSA would have been motivated to use liposomal irinotecan (MM-398) in place of the free irinotecan in Conroy/FOLFIRINOX. As an initial matter, Patent Owner admits that irinotecan and liposomal irinotecan are, from a qualitative safety standpoint, considered similar. (Ex. 1015 at ¶¶ 231-235; see also id. at 225 (admitting they similarly lack drug interaction with 5FU/LV); Ex. 1006 at 21 (same).) Therefore, a POSA would have considered this substitution. Ko and Saif, discussed in Sections VIII (E-F) above, also support this understanding and/or provide a POSA with additional motivation to combine, i.e., they suggest studying and/or replacing free irinotecan with liposomal irinotecan. Consistently, Saif also specifically states that because of these encouraging results of using MM-398 in second-line therapy, "it seems ***logical*** to test this drug/regimen further: **will it be worth replacing irinotecan in FOLFIRINOX with MM-398**." (Ex. 1007 at 1 (emphasis added).) As with Saif, Ko also suggested that given the emergence of FOLFIRINOX as a first-line standard in advanced pancreatic cancers, MM-398 should be further explored in the first-line therapy setting. (Ex. 1008 at 5.)

236. In addition, Bayever suggests such a substitution and provides even further motivation to combine, as Bayever and other prior art disclosed evidence of

superiority of liposomal irinotecan to irinotecan. (See Ex. 1006 at 11, 19-21, 25; Ex. 1008 at 2-5; Exs. 1058-1059.) Bayever suggests its liposomal formulation of irinotecan "has several attributes that may provide an improved therapeutic index," therapeutic synergy, or "superior outcome." (Id. at 5, 10, 16.) Bayever disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims (60 mg/m^2) along with the same claimed doses of leucovorin (i.e., 200 mg/m^2 of the (*l*)-form or 400 mg/m^2 of the (*l*+*d*) racemic form) and 5-FU (i.e., 2,400 mg/m^2)). (Id. at 4, 6, 14-15, 26-27, 32-33, 39-42, 54, 63.)

237. Bayever disclosed that MM-398 administration results in a 20-fold increase in tumor AUC_{SN-38} for MM-398 compared to free irinotecan. (Id. at 20.) The long duration of exposure allows for prolonged exposure of the slow-proliferating cancer cells to the active metabolite SN-38 as they progress through the cell cycle. (Id.) Bayever also disclosed that MM-398 has several attributes that may provide an improved therapeutic index, including local bioactivation that results in reduced drug exposure at potential sites of toxicity, increased exposure at cancer cells within the tumor, and potentially greater susceptibility of tumors to agents such as 5-FU/LV. (Id. at 20-21.)

238. Even in the absence of other motivations, a POSA would have understood that Bayever would motivate a POSA to substitute liposomal irinotecan

for free irinotecan in regimens like FOLFIRINOX. For example, Bayever discloses that MM-398 alone and in combination with leucovorin and 5-FU "are useful for the treatment of all pancreatic cancers, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments," and pancreatic cancers exhibiting "either or both of distant metastasis or peripancreatic extension of the tumor." (Ex. 1006 at 13.) (A POSA would also know that the combination disclosed in Bayever had been successful as based on Saif.) Thus, in view of at least the above teachings of Bayever, a POSA would have understood that MM-398 alone and in combination with leucovorin and 5-FU can be used in first line, second-line or third-line therapy, or initial or add-on combination therapy or replacement therapy, such as in the first-line FOLFIRINOX region for treating metastatic pancreatic cancer. Furthermore, a POSA would also have understood that MM-398 had pharmacological properties and advantages that could result in clinical superiority to free irinotecan. (See, e.g., Supra Section VII.E (identifying and listing several purported advantages of MM-398 suggesting the superiority of MM-398 and that it works better than free irinotecan).)

239. A POSA would have therefore been motivated to replace free irinotecan in the FOLFIRINOX regimen with liposomal irinotecan. Bayever discloses doses of 80 mg/m^2 liposomal irinotecan in some regimens but recommends lowering that dose to 60 mg/m^2 for those with toxicity concerns, including for patients

homozygous for the *UGT1A1*28* allele. (Supra Sections VII.D.c; VIII.E.) Therefore, a POSA would have understood that doses of liposomal irinotecan in the range of 60-80 mg/m^2 were tolerable in most patients but that 80 mg/m^2 was probably not tolerable in patients homozygous for the *UGT1A1*28* allele (as well as other known poor metabolizer alleles).

240. A POSA would have found any dose within the 60-80 mg/m^2 an obvious option for future study. In addition, a POSA—with an aim to reduce toxicity of the FOLFIRINOX regimen, as taught by at least Conroy, Conroy Protocol, and Conroy 2013—would have certainly considered a starting dose of 60 mg/m^2 as taught by Bayever. (See Ex. 1006 at 4; Sections VIII.A-C, E.) This is consistent with the dose reduction of MM-398 to 60 mg/m^2 by Bayever when patients experience an adverse event. (Ex. 1006 at 39-42.)

241. Second, given the toxicity of FOLFIRINOX, a POSA would be motivated to also lower the 85 mg/m^2 dose of oxaliplatin to reduce toxicity concerns. Notably, Conroy and Conroy Protocol taught the potential need for reduction of the oxaliplatin dose. For example, Conroy disclosed that a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m^2 oxaliplatin was used in the study, indicating in many patients a lower dose of oxaliplatin was administered. (Section VIII.A; Ex. 1003 at 4.) The Conroy Protocol also disclosed a dose reduction of oxaliplatin to 60 mg/m^2 oxaliplatin for toxicity. (Ex. 1004 at 16-18, 27.) A POSA

who reviewed the results of Conroy stating that the median dose intensity of oxaliplatin was 78% and the fact that the Conroy Protocol disclosed numerous dose reductions of oxaliplatin to 60 mg/m^2 oxaliplatin in the event of certain toxicity incidents would have concluded that a significant portion of patients undergoing the FOLFIRINOX trial were administered oxaliplatin 60 mg/m^2. In addition, because a POSA would have been motivated to substitute MM-398 for the free irinotecan in FOLFIRINOX, an effective but toxic regimen, a POSA would have been cautious about oxaliplatin dosing. A POSA would therefore have considered lowering the oxaliplatin dose through routine optimization.

242. Based on the disclosures in the prior art, a POSA would have understood that doses of oxaliplatin in the range of 60-80 mg/m^2 were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m^2 FOLFIRINOX dose. Because most dosing is done in increments of 5 mg/m^2, a POSA would have a limited number of tolerable doses to choose from and found any dose within that range an obvious choice. In addition, a POSA would have been aware of the 60 mg/m^2 dose of oxaliplatin disclosed in the Conroy protocol. (See Section VIII.B.) A POSA would have been motivated to select a dose that had already been used or tested. (See id; see also Section VIII.H (also disclosing a 60 mg/m^2 dose of oxaliplatin). Moreover, a POSA would have understood that other art, like Cantore, showed or suggested that these lower dose

regimens, including a 60 mg/m^2 dose of oxaliplatin along with 60 mg/m^2 irinotecan, were found to be safe and effective in metastatic pancreatic cancer patients.

243. Furthermore, a POSA would have known that oxaliplatin was part of standard prior art regimens (e.g., FOLFIRINOX, FOLFOX) in treating various cancers, including metastatic pancreatic cancer, and methods of determining a tolerable and effective dose of oxaliplatin were already established in standard first-line therapies such as FOLFIRINOX. (See Section VIII.)

244. Third, a POSA would also have known that a modification of the 5-FU dose would also improve the toxicity profile. Specifically, a POSA would have known of Mahaseth et al. (and others, as reviewed in Conroy 2013) who developed a modified FOLFIRINOX regimen by discontinuing the 400 mg/m^2 bolus of 5-FU from the FOLFIRINOX regimen. (Ex. 1005 at 2). This modified regimen was well tolerated and improved the safety profile of the original FOLFIRINOX regimen with respect to neutropenia, fatigue, and vomiting. (Id. at 4.) It also maintained FOLFIRINOX's overall efficacy, with progression-free survival (PFS) and overall survival (OS) of 13.7 and 17.8 months, respectively. (Id.) Mahaseth concluded that this "modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC (pancreatic cancer)." (Id. at 5.) A POSA would have been motivated to reduce Conroy's 5-FU dose to achieve these same benefits.

245. A comparison between the antineoplastic therapy of claim 1 and the teachings of Conroy, Conroy Protocol, Mahaseth, and Bayever is provided in the chart below:

Claim 1 of the '552 patent	**Prior Art**
1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient 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 (1)-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.	**Conroy, Conroy Protocol,** and **Mahaseth** disclose: The FOLFIRINOX 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: 246. 60 mg/m^2 oxaliplatin, 247. 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 248. 2,400 mg/m^2 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient. **Bayever** discloses: 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: 249. 60 mg/m^2 of liposomal irinotecan, 250. 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

Claim 1 of the ’552 patent	Prior Art
	251. 2,400 mg/m^2 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.

252. As can be seen from the above chart, a combination of Conroy, Conroy Protocol, Mahaseth, and Bayever teaches each and every feature of claim 1.

253. I am also aware of the unexpected result arguments put forth by the applicant of the ’552 patent during prosecution. (Ex. 1119 at 151; see also Section IX.B (discussing alleged unexpected results and reliance on post-filing Wainberg reference).)

254. However, as explained herein, such a result is hardly unexpected. Since it has been universally accepted in the prior art that providing lower doses of these chemotherapy drugs, including oxaliplatin, would result in fewer side effects, a POSA would have expected that the claimed doses of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin (60/60) would confer better safety and tolerability than doses of 60 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin (60/85) as suggested by Conroy and Conroy Protocol in view of Mahaseth and Bayever.

255. Wainberg merely reveals that the 60/60 regimen was selected because it showed one less patient (one out of seven) exhibiting a dose limiting toxicity (DLT) over the 60/85 regimen (two out of ten). (Ex. 1018 at 19). No POSA would

consider the difference between the 60/60 regimen and the 60/85 regimen to be a difference in kind, as the difference is most likely attributable to chance rather than any difference in DLT.

256. Patent Owner then argued that the 60/60 regimen "unexpectedly resulted in primary efficacy outcomes higher than that of the currently preferred FOLFIRINOX regimen as reported in Conroy" and concluded "[t]hese improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen." [Ex. 1119 at 153 (emphasis added)]. However, as I explained below, this argument regarding efficacy outcomes is seriously flawed.

257. First, Wainberg et al. (Wainberg, *et al.*, European Journal of Cancer, 151:14-24 (2021)) ("Wainberg 2021" (Ex. 1019)) made it clear that no such comparisons can be made between its results and those of FOLFIRINOX because of the inherent limitations of its study. In fact, Wainberg et al. stated that they "cannot be reliably compared with that of established therapies without head-to-head studies," and that "direct comparisons" between the two studies "cannot be made," especially in view of the "[l]imitations inherent in [Wainberg's] study design includ[ing] the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomized design; and the absence of a control group." (Ex. 1019 at 8.) Wainberg highlights that

"important differences between the study populations include the proportions of patients with metastatic disease at study entry…, the proportions with liver metastases…, and the median ages," where the FOLFIRINOX patients were older and had a higher proportion of metastatic disease. (Id.*)* The statements by Wainberg teach a POSA that any apparent differences may be due to chance, and therefore certainly could not be considered a difference in kind.

258. Subsequent studies have further addressed this issue by analyzing larger data sets. Nichetti et al. compared clinical trial results for NALIRIFOX (an embodiment of the claims of the '552 patent) against FOLFIRINOX (prior art regiment) in first-line therapy for metastatic pancreatic cancer patients, and reported that there was "**no difference observed**" in overall survival between NALIRIFOX (11.1 months) and FOLFIRINOX (11.7 months), and "[a]nalysis of 6- and 12-month OS did not find statistically significantly higher OS for NALIRIFOX compared with FOLFIRINOX." (Ex. 1010 at 1, 5.) These results led Nichetti et al. to conclude "NALIRIFOX failed to break the symbolic wall of 12 months of median OS, thus questioning the real improvement shown in the NAPOLI 3 trial," and "Ultimately, our data do not suggest a preference between NALIRIFOX and FOLFIRINOX." (Id. at 9, 10.)

259. Similarly, Nevala-Plagemann states that in comparison with the PRODIGE 4 (containing a FOLFIRINOX arm), "NALIRIFOX does not seem to

raise the bar, but rather exposes patients and health-care systems to financial toxicities," and "A recently published systematic review and meta-analysis supports our conclusion that the differences in OS between NALIRIFOX and modified FOLFIRINOX are not clinically significant and that those in neuropathy are not statistically significant." (Ex. 1011 at 1, 2 (emphases added).) More specifically, Nevala-Plagemann reports that the "median OS [overall survivability] of patients receiving NALIRIFOX in NAPOLI 3 is identical to that of those who received FOLFIRINOX in PRODIGE 4 (11.1 months)." (Id. at 567 (emphasis added).) With regard to toxicity, Nevala-Plagemann further states "6.5% of patients receiving NALIRIFOX had grade ≥3 peripheral neuropathy (3% peripheral neuropathy and 3.5% peripheral sensory neuropathy) compared to 9% of patients receiving FOLFIRINOX in PRODIGE 4, a clinically insignificant difference." (Id. at 2 (emphasis added).)

260. Importantly, a POSA would recognize that Nichetti and Nevala-Plagemann do not share the inherent limitations of Wainberg (relied upon during prosecution) because their analyses are more comprehensive, and not focused on a single clinical trial. Moreover, Nichetti and Nevala-Plagemann clearly refute Patent Owner's argument that the regimen of the claims of the '552 patent exhibited unexpected results, at least because the claimed regimen yielded identical or

clinically insignificant efficacy differences as compared to the prior art FOLFIRINOX first-line therapy.

261. Finally, even if the claimed regimen were deemed to be in some way superior to the closest prior art (FOLFIRINOX, as disclosed in Ex. 1003), a POSA would not have found that result to have been unexpected, since Bayever taught that liposomal irinotecan was superior to free irinotecan, and therefore a POSA would have expected the claimed regimen to be superior to FOLFIRINOX. This opinion is supported by Saif and Ko, who both were excited about such a substitution, in hopes of improving the overall survival of patients with pancreatic cancer.

262. Taken together, in my opinion, a POSA would have understood that the benefits of the NALIRIFOX regimen, if any, would not support non-obviousness of the regimens of the claims of the ’552 patent.

263. I understand that no additional secondary considerations were asserted during prosecution. I reserve the right to address any secondary considerations set forth by Patent Owner in any later response to this declaration or the petition it accompanies.

264. Therefore, for at least the foregoing, claim 1 of the ’552 patent is obvious at least over the references discussed above.

b. Claim 3

265. In my opinion, claim 3 of the ’552 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites “the 5-fluorouracil is administered as an infusion over 46 hours.”

266. Both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (Ex. 1003 at 3; Ex. 1005 at 2.) In addition, Bayever also discloses “5-FU is administered intravenously over 46 hours.” (Ex. 1006 at 5, 6, 13, 26.)

267. Accordingly, claim 3 of the ’552 patent would have been obvious to a POSA over the prior art.

c. Claim 4

268. In my opinion, claim 4 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 4 depends from claim 1 and recites, “the leucovorin is administered immediately prior to the 5-fluorouracil.”

269. Conroy, Mahaseth, and Bayever all disclose that the LV is administered immediately prior to 5-FU. (Ex. 1003 at 3; Ex. 1005 at 2; Ex. 1006 at 27.) In particular, Bayever discloses “leucovorin should always be administered prior to 5-

FU." (Ex. 1006 at 27 and claim 4). Therefore, it was known to administer LV immediately prior to the 5-FU.

270. Accordingly, claim 4 of the '552 patent would have been obvious to a POSA over the prior art.

d. Claim 5

271. In my opinion, claim 5 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 5 depends from claim 1 and recites, "the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle."

272. Conroy discloses that irinotecan, oxaliplatin, and leucovorin were administered every two weeks, which corresponds to days 1 and 15. (Ex. 1003 at 3.) Conroy also discloses that six months of chemotherapy was recommended for patients who had a response, which constitutes at least one 28-day treatment cycle. Similarly, Bayever also discloses that liposomal irinotecan MM-398 and leucovorin were also administered at least one cycle with a period of 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated "until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (Ex. 1006 at 6, 14, 15, 26-27.) Therefore, it was known to a POSA to administer liposomal irinotecan, oxaliplatin, 5-FU and LV on days 1 and 15 of a 28-day treatment cycle.

273. Accordingly, claim 5 of the ’552 patent would have been obvious to a POSA over the prior art.

e. Claim 6

274. In my opinion, claim 6 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 6 depends from claim 1 and recites, “the liposomal irinotecan is administered as an infusion over about 90 minutes.”

275. Bayever discloses that MM-398 is administered as an infusion over 90 minutes. (Ex. 1006 at 5, 6, 13, 26-27, 33 and claims 6, 15.) Therefore, a POSA motivated to incorporate MM-398 into Conroy would have considered administering it as an infusion over 90 minutes.

276. Accordingly, claim 6 of the ’552 patent would have been obvious to a POSA over the prior art.

f. Claim 8

277. In my opinion, claim 8 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 8 depends from claim 2 and recites, “the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.”

278. Bayever discloses MM-398 (also known as PEP02), which is irinotecan sucrose octasulfate encapsulated in liposomes. (Ex. 1006 at 4-7, 9 (stating that

"irinotecan is administered in a stable liposomal formulation as irinotecan sucrose sulfate liposome injection (otherwise termed 'irinotecan sucrose octasulfate salt liposome injection')").

279. Accordingly, claim 8 of the '552 patent would have been obvious to a POSA over the prior art.

g. Claim 9

280. In my opinion, claim 9 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 9 depends from claim 1 and recites "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)."

281. Bayever discloses that MM-398, also known as PEP02, is irinotecan sucrose sulfate liposome as described in the '867 patent. (Ex. 1006 at 9.) The irinotecan sucrose sulfate liposome contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypoly ethlyeneglycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE). (Ex. 1006 at 9; Ex. 1024 at 27:46-51; 91:13-18 and claim 31.)

282. Accordingly, claim 9 of the '552 patent would have been obvious to a POSA over the prior art.

h. Claim 10

283. In my opinion, claim 10 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 10 depends from claim 1 and recites, “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).”

284. Bayever discloses that MM-398, also known as PEP02, is irinotecan sucrose sulfate liposome as described in the ’867 patent. (Ex. 1006 at 9.) The irinotecan sucrose sulfate liposome contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypoly ethlyeneglycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE). (Ex. 1006 at 9; Ex. 1024 at 27:46-51; 91:13-18 and claim 31.)

285. Accordingly, claim 10 of the ’552 patent would have been obvious to a POSA over the prior art.

i. Claim 11

286. In my opinion, claim 11 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claims 1, 3-5, and 10. Claim 11 depends from claim 10 and recites, “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."

287. Conroy discloses that irinotecan, oxaliplatin, and LV were administered every two weeks, which corresponds to days 1 and 15. (Ex. 1003 at 3.) Conroy also discloses that six months of chemotherapy was recommended for patients who had a response, which constitutes at least one 28-day treatment cycle. Similarly, Bayever also discloses that liposomal irinotecan MM-398 and LV were also administered at least one cycle with a period of 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated "until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (Ex. 1006 at 6, 14, 15, 26-27.)

288. Bayever discloses, "in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU. (Ex. 1006 at 13, 14, 33 and claim 4.)

289. Conroy, Mahaseth, and Bayever all disclose that the LV is administered immediately prior to 5-FU. (Ex. 1003 at 3; Ex. 1005 at 2; Ex. 1006 at

27.) In particular, Bayever discloses "leucovorin should always be administered prior to 5-FU." (Ex. 1006 at 27 and claim 4).

290. Both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (Ex. 1003 at 3; Ex. 1005 at 2.) Similarly, Bayever also discloses "5-FU is administered intravenously over 46 hours." (Ex. 1006 at 5, 6, 13, 26.)

291. Accordingly, claim 11 of the '552 patent would have been obvious to a POSA over the prior art.

j. Claim 12

292. In my opinion, independent claim 12 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 12 recites:

> 12. 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 (1)-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.

293. A comparison of claim 1 and claim 12 is provided in the chart below. As shown, claim 12 further specifies an antineoplastic agent as gemcitabine.

Claim 1	**Claim 12**
1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient **who has not previously received an antineoplastic agent** to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient 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 (1)-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.	12. 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 (1)-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.

294. A POSA would have understood that gemcitabine is an antineoplastic agent, and the FOLFIRINOX regimens of Conroy and Mahaseth were administered as first-line therapy in patients who had not been previously treated with gemcitabine. (Ex. 1003 at 1; Ex. 1005 at 1.) Thus, claim 12 would also have been obvious to a POSA based on the above discussion with respect to claim 1 and in view of the prior art.

k. Claim 13

295. In my opinion, claim 13 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claims 1 and 11. Claim 13 depends from claim 1 and recites, “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.”

296. Conroy discloses that irinotecan, oxaliplatin, 5-FU and LV were administered every two weeks, which corresponds to days 1 and 15. (Ex. 1003 at 3.) Conroy also discloses that six months of chemotherapy was recommended for patients who had a response, which constitutes at least one 28-day treatment cycle. Similarly, Bayever also discloses that liposomal irinotecan MM-398 and leucovorin were also administered at least one cycle with a period of 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated “until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (Ex. 1006 at 6, 14, 15, 26-27.)

297. Bayever discloses "in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU. (Ex. 1006 at 13, 14, 33 and claim 4.)

298. Conroy, Mahaseth, and Bayever all disclose that the leucovorin is administered immediately prior to 5-FU. (Ex. 1003 at 3; Ex. 1005 at 2; Ex. 1006 at 27.) In particular, Bayever discloses "leucovorin should always be administered prior to 5-FU." (Ex. 1006 at 27 and claim 4).

299. Both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (Ex. 1003 at 3; Ex. 1005 at 2.) Similarly, Bayever also discloses "5-FU is administered intravenously over 46 hours." (Ex. 1006 at 5, 6, 13, 26.)

300. Therefore, it was known to a POSA to administer the liposomal irinotecan, oxaliplatin, LV, and 5-FU beginning on days 1 and 15 of a 28-day treatment cycle and to administer liposomal irinotecan prior to each administration of the LV, to administer LV prior to each administration of the 5-FU, and to administer the 5-FU as an infusion over 46 hours.

301. Accordingly, claim 13 of the '552 patent would have been obvious to a POSA over the prior art.

l. Claim 14

302. In my opinion, claim 14 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claims 12, 11, and 13. Claim 14 depends from claim 12 and recites, “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.”

303. Conroy discloses that irinotecan, oxaliplatin, 5-FU and LV were administered every two weeks, which corresponds to days 1 and 15. (Ex. 1003 at 3.) Conroy also discloses that six months of chemotherapy was recommended for patients who had a response, which constitutes at least one 28-day treatment cycle. Similarly, Bayever also discloses that liposomal irinotecan MM-398, 5-FU and LV were also administered at least one cycle with a period of 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated “until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (Ex. 1006 at 6, 14, 15, 26-27.)

304. Bayever discloses "in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU." (Ex. 1006 at 13, 14, 33 and claim 4.)

305. Conroy, Mahaseth, and Bayever all disclose that the LV is administered immediately prior to 5-FU. (Ex. 1003 at 3; Ex. 1005 at 2; Ex. 1006 at 27.) In particular, Bayever discloses "leucovorin should always be administered prior to 5-FU." (Ex. 1006 at 27 and claim 4).

306. Both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (Ex. 1003 at 3; Ex. 1005 at 2.) Similarly, Bayever also discloses "5-FU is administered intravenously over 46 hours." (Ex. 1006 at 5, 6, 13, 26.)

307. Accordingly, claim 14 of the '552 patent would have been obvious to a POSA over the prior art.

B. GROUND 2: CLAIMS 7 AND 15 WOULD HAVE BEEN OBVIOUS IN VIEW OF THE PRIOR ART DISCLOSED IN GROUND 1 IN FURTHER VIEW OF MASI AND GINOCCHI

a. Claim 7

308. In my opinion, claim 7 of the '552 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 2. Claim 7 depends from claim 1 and recites, "the liposomal irinotecan is administered,

followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil."

309. Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen immediately following administration of leucovorin. (Ex. 1003 at 1; Ex. 1005 at 2.) Similarly, Bayever also discloses that 5-FU is administered last, immediately following administration of LV. (Ex. 1006at 13, 14, 33 and claims 4 and 14.) Moreover, as discussed above, this claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients. (Ex. 1016at 1.)

b. Claim 15

310. In my opinion, claim 15 of the '552 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1 of Ground 1 and Ground 2. Claim 15 depends from claim 1 and recites, "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."

311. Bayever additionally discloses that the patient is pre-medicated with dexamethasone, which is a corticosteroid, and an ant-emetic to the patient prior to the antineoplastic therapy. (Ex. 1006 at 5, 6, 33, 35, 45 and claims 9 and 18.)

Therefore, administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy was known to a POSA, and standard medical practice.

C. GROUND 3: CLAIMS 1 AND 3-15 WOULD HAVE BEEN OBVIOUS BASED ON THE PRIOR ART DISCUSSED IN GROUNDS 1 AND 2 AND IN FURTHER VIEW OF CARNEVALE, AND/OR DEAN

312. In my opinion, claims 1-15 would have been obvious based on the prior art discussed in Grounds 1 and 2 and in view of Carnevale, and/or Dean. Carnevale, and/or Dean are discussed as prior art under Ground 3 if the earliest filing date of the ’552 patent is November 10, 2017.

a. Claim 1

313. In my opinion, claim 1 of the ’552 patent would also have been obvious for at least the reasons set forth above with respect to claim 1 of Ground 1 and further in view of the teachings of Carnevale, and Dean. I hereby incorporate my analysis with respect to Ground 1 above.

314. Dean discloses a phase 2 clinical trial that evaluates the safety and efficacy of liposomal irinotecan MM-398 with 5-FU, leucovorin, and oxaliplatin in first-line therapy of pancreatic cancer patients.

315. Carnevale discloses that based on the optimized pharmacokinetics and safety profile of MM-398, MM-398 liposomal irinotecan would “make an ideal substitute for irinotecan in the first-line FOLFIRINOX regimen” and that “this might

represent a natural extension of MM-398's role in metastatic pancreatic cancer." (Ex. 1013 at 11 (emphasis added).)

316. Thus, NCT02551991, Dean, and/or Carnevale provide further motivation to a POSA to substitute the prior art MM-398 liposomal irinotecan with free irinotecan in the established gold-standard FOLFIRINOX regimen at the claimed doses and frequency.

317. Accordingly, for at least the reasons discussed above, claim 1 of the '552 patent is obvious.

b. Claim 3

318. In my opinion, claim 3 is obvious for at least the reasons set forth above with respect to claims 1 and 3 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

c. Claim 4

319. In my opinion, claim 4 is obvious for at least the reasons set forth above with respect to claims 1 and 4 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

d. Claim 5

320. In my opinion, claim 5 is obvious for at least the reasons set forth above with respect to claims 1 and 5 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

e. Claim 6

321. In my opinion, claim 6 is obvious for at least the reasons set forth above with respect to claims 1 and 6 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

f. Claim 7

322. In my opinion, claim 7 is obvious for at least the reasons set forth above with respect to claim 1 of Ground 1, claim 7 of Ground 2, and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Grounds 1 and 2 above.

g. Claim 8

323. In my opinion, claim 8 is obvious for at least the reasons set forth above with respect to claims 1 and 8 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

h. Claim 9

324. In my opinion, claim 9 is obvious for at least the reasons set forth above with respect to claims 1 and 9 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

i. Claim 10

325. In my opinion, claim 10 is obvious for at least the reasons set forth above with respect to claims 1 and 19 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

j. Claim 11

326. In my opinion, claim 11 is obvious for at least the reasons set forth above with respect to claims 1, 3, 10, and 11 of Ground 1 and Claim 1 in Ground 3. I hereby incorporate my analysis with respect to Ground 1.

k. Claim 12

327. In my opinion, claim 12 is obvious for at least the reasons set forth above with respect to claims 1 and 12 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

l. Claim 13

328. In my opinion, claim 13 is obvious for at least the reasons set forth above with respect to claims 1, 3, and 13 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

m. Claim 14

329. In my opinion, claim 14 is obvious for at least the reasons set forth above with respect to claims 1, 3, 12, 13, and 14 of Ground 1 and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Ground 1.

n. Claim 15

330. In my opinion, claim 15 is obvious for at least the reasons set forth above with respect to claims 1 of Ground 1, claims 2 and 15 of Ground 2, and claim 1 of Ground 3. I hereby incorporate my analysis with respect to Grounds 1 and 2 above.

XI. CONCLUSION

331. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

332. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Signature: 

Mark J. Ratain, MD

Date: January 17, 2025

Appendix A

MARK J. RATAIN, MD, FASCO

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Telephone: (773) 795-5453

Education

1976	Harvard University, A.B. (biochemical sciences, magna cum laude)
1980	Yale University School of Medicine, M.D. (thesis -"Elicitation of the late nasal and cutaneous response: the possible role of eosinophils and basophils")

Professional Positions

1972-1977	Computer programmer/systems analyst - part-time. System Sciences, Inc., Bethesda, MD
1980-1981	Intern, Osler Medical Service, Johns Hopkins Hospital, Baltimore, MD
1981-1983	Resident, Osler Medical Service, Johns Hopkins Hospital, Baltimore, MD
1983-1986	Fellow, Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, IL
1986-1988	Associate Attending Member, Department of Medicine, Division of Hematology/Oncology, Michael Reese Hospital and Medical Center, Chicago, IL
1986-1987	Instructor, Department of Medicine, Section of Hematology/Oncology, and Committee on Clinical Pharmacology, The University of Chicago, Chicago, IL
1987-1991	Assistant Professor, Department of Medicine, Section of Hematology/Oncology, and Committee on Clinical Pharmacology, The University of Chicago, Chicago, IL
1988-1989	Attending Member, Department of Medicine, Division of Hematology/Oncology, Michael Reese Hospital and Medical Center, Chicago, IL
1988-1992	Director of Clinical Pharmacology, Section of Hematology/Oncology, The University of Chicago, Chicago, IL
1991-1995	Director, Developmental Therapeutics Program, Cancer Research Center, The University of Chicago, Chicago, IL
1991-1995	Associate Professor, Department of Medicine, Section of Hematology/Oncology, Committee on Clinical Pharmacology, and Cancer Research Center, The University of Chicago, Chicago, IL

1992-2010	Chairman, Committee on Clinical Pharmacology and Pharmacogenomics[*], The University of Chicago, Chicago, IL
1995-2002	Professor, Department of Medicine, Section of Hematology/Oncology, Committee on Clinical Pharmacology and Pharmacogenomics[*], and Cancer Research Center, The University of Chicago, Chicago, IL
1995-2000	Co-Director, Clinical and Experimental Therapeutics Program, Cancer Research Center, The University of Chicago, Chicago, IL
1999-2022	Associate Director for Clinical Sciences, Comprehensive Cancer Center[t], The University of Chicago, Chicago, IL
2002-	**Leon O. Jacobson Professor, Department of Medicine, Section of Hematology/Oncology, Committee on Clinical Pharmacology and Pharmacogenomics[*], and Comprehensive Cancer Center[t], The University of Chicago, Chicago, IL**
2010-	**Director, Center for Personalized Therapeutics, The University of Chicago, Chicago, IL**
2010-	**Chief Hospital Pharmacologist, The University of Chicago Medicine[&], Chicago, IL**

[*]previously Committee on Clinical Pharmacology
[t]previously Cancer Research Center
[&]previously University of Chicago Medical Center

Federal Research Review and Service

National Institutes of Health
- Ad Hoc Reviewer, Experimental Therapeutics Study Section, Division of Research Grants 1986
- Special Review Committee, National Cancer Institute 1991
- Consultant Reviewer, Department of Veteran Affairs 1993
- Ad Hoc Reviewer, National Cancer Institute 1993, 2019
- Special Study Section (Small Business Innovative Research Program), Division of Research Grants 1994
- Ad Hoc Reviewer, National Center for Research Resources 1997
- Reviewer, Intramural Review Office, Pediatric Oncology Branch, National Cancer Institute 1998
- Clinical Oncology Special Emphasis Panel, Oncological Science Initial Review Group, Center for Scientific Review 1999-2000
- Clinical Advisory Working Group, National Institute of General Medical Sciences 1999
- Ad Hoc Reviewer, Drug Development Group, National Cancer Institute 2000, 2001
- Data and Safety Monitoring Board (T-Cell Depleted Auto Stem Cell Transplant Trial for Systemic Sclerosis), National Institute of Arthritis and Musculoskeletal Diseases 2002-2005
- Clinical Trials Working Group, National Cancer Advisory Board, National Cancer Institute 2004-2005
- Investigational Drug Steering Committee, National Cancer Institute 2005-2016 (Co-Chair, Steering Committee, 2005-2008; Co-Chair, Clinical Trials Design Task Force, 2012-2016)
- National Institute of General Medical Sciences Special Emphasis Panel 2006
- Subcommittee J - Population and Patient-Oriented Training, National Cancer Institute Initial Review Group (Ad Hoc Reviewer 2006; Member 2006-2009)
- Reviewer, NIH Director's New Innovator Awards 2008
- Reviewer, Center for Scientific Review 2010
- National Institute of General Medical Sciences Special Emphasis Panel 2013, 2014, 2018
- National Cancer Institute Special Emphasis Panel 2020, 2021
- National Institute of Child Health and Human Development 2023

Other Research Review Activities

Dutch Cancer Society
- Ad Hoc Reviewer 1994, 1999

The Cancer Society of New Zealand
- Ad Hoc Reviewer 1994

Joint Infrastructure Fund, Wellcome Trust
- Ad Hoc Reviewer 1998, 2000

Institut National du Cancer
- Ad Hoc Reviewer 2010, 2019, 2021

Christian Doppler Research Association
- Ad Hoc Reviewer 2011

Pennsylvania Department of Health
- Ad Hoc Reviewer 2012-2014, 2016-2017, 2022

Florida Department of Health
- Ad Hoc Reviewer 2015-2016, 2021, 2022, 2023

Cancer Research UK
Ad Hoc Reviewer 2018-2019

Nazarbayev University Research Review
Ad Hoc Reviewer 2020

Sternfels Prize
Judging Panel 2021, 2022

United Arab Emirates University
Ad Hoc Reviewer 2021

Netherlands Organization for Health Research and Development
Ad Hoc Reviewer, 2022

Fondazione Gianni Bonadonna
Ad Hoc Reviewer, 2024

National and International Organizations

Cancer and Leukemia Group B
Chemotherapy Committee 1988-1990
Breast Committee 1989-1998
Ad Hoc Committee on Relations with Pharmaceutical Companies 1989-1990
Pharmacology and Experimental Therapeutics Committee 1990-2011 (Chair, 1994-2011)
Ad Hoc Nominating Committee 1989-1990
Industrial Relations Committee 1992-1993
Executive Committee 1993-1996
Board of Directors 1993-2011
Chair, Ad Hoc Committee on Conflict of Interest 1994-1996
Chair, Conflict of Interest Committee 1996-1998

American Federation for Clinical Research
Medical School Representative 1988-1989

American Society for Clinical Pharmacology and Therapeutics
Hematologic and Neoplastic Diseases Section Vice Chair, 1988-1992; Chair, 1992-1995
Government Affairs Committee 1990-2002 (Vice Chair, 1997-2002)
Long Range Planning Committee 1990-1993
Committee on Coordination of Scientific Sections 1992-1995, 1998-2001 (Chair, 1998-2001)
Scientific Program Committee 1993-1994, 1996-1998, 2001-2004 (Vice Chair 2001-2002, Chair 2002-2003, Immediate Past Chair 2003-2004)
Nominating Committee 1995-1996
Board of Directors 1997-2001
Executive Committee 1998-2001
Communications and Public Relations Committee 1998-2001
Committee on Substance Abuse 1998-2001
Membership Committee 2000-2003
Best Practices Task Force 2017-2018

International Workshops on Pharmacodynamics of Anticancer Agents
- First International Workshop on Pharmacodynamics of Anticancer Agents (Fontana, WI), Co-Organizer 1989
- Second International Workshop on Pharmacodynamics of Anticancer Agents (Eze, France), Co-Organizer 1992
- Third International Workshop on Pharmacodynamics of Anticancer Agents (Irvington, VA), Co-Organizer 1995
- Fourth International Workshop on Pharmacodynamics of Anticancer Agents (Dunkeld, Scotland), Co-Organizer 1998
- Fifth International Workshop on Pharmacodynamics of Anticancer Agents (Sea Island, GA), Co-Organizer 2001
- Sixth International Workshop on Pharmacodynamics of Anticancer Agents (Venice, Italy), Co-Organizer 2004
- Seventh International Workshop on Pharmacodynamics of Anticancer Agents (Guanacaste, Costa Rica), Co-Organizer 2007
- Eighth International Workshop on Pharmacodynamics of Anticancer Agents (Hakone, Japan), Co-Organizer 2010
- Ninth International Workshop on Pharmacodynamics of Anticancer Agents (Hexham, England), Co-Organizer 2013
- Tenth International Workshop on Pharmacodynamics of Anticancer Agents (Skamania, WA), Co-Organizer 2016
- Eleventh International Workshop on Pharmacodynamics of Anticancer Agents (Monestier, France), Co-Organizer 2019
- Twelfth Intenational Workshop on Pharmacodynamics of Anticancer Agents (Ponta Delgada, Portugal), Co-Organizer 2024

American Society of Clinical Oncology
- Committee for Patient Advocacy 1990-1992
- Audit and Finance Committee 1990-1994 (Chair, 1990-1994)
- Secretary-Treasurer 1994-1997
- Board of Directors 1994-1997
- Executive Committee 1994-1997
- Strategic Planning Committee 1994-1998
- Program Committee 1995-1997, 1998-2000 (Subchair for Clinical Pharmacology, 1995-1996; Board Liaison, 1995-1996)
- Industry/Exhibits Committee 1995-1997 (Board Liaison, 1995-1997)
- Ad Hoc Committee to Develop ASCO OnLine 1995
- Clinical Methods Workshop Program Committee 1995-1997
- OnLine Committee 1995-2000
- Subcommittee on Phase I Clinical Trials, Public Issues Committee 1996 (Chair, 1996)
- Publications Committee 1997-2000 (OnLine Committee Liaison 1997-2000)
- Continuing Medical Education Committee 1997-2000 (Chair, 1997-1999; Immediate Past Chair, 1999-2000)
- Cancer Education Committee 2000-2003 (Track Team Leader, Pharmacology/Drug Development, 2002-2003)
- Translational Research Task Force 2005
- Cancer Research Committee 2007-2010 (Chair, Pre-Phase III Working Group 2008-2010)
- ASCO Workshop on Exploratory Research Biopsies Planning Committee 2018 (Chair)

European Organization for Research and Treatment of Cancer
- Pharmacology and Molecular Mechanisms Group (Corresponding Member) 1990-2004

National Board of Medical Examiners
Step 3 Test Material Development Committee for Utilization of Resources, United States Medical Licensing Examination 1997-1998

Pharmacogenomics (previously Pharmacogenetics) of Anticancer Agents Research Group
Founding Chair 2000-2015

Pharmacogenomics (previously Pharmacogenetics) Research Network
Steering Committee 2000-2015, 2018-2020 (Chair, 2000-2003)
Coordinating Committee 2003-2004, 2007-2008
Cancer Partnerships Working Group 2006-2010 (Co-Chair, 2006-2010)

U.S. Pharmacopeia
Oncologic Disease Expert Committee 2000-2003

Institut Pasteur Euroconferences
Pharmacogenomics 2, Scientific Committee 2001-2002

American Board of Clinical Pharmacology
Governing Board 2002-2007
Credentials Committee 2002-2007 (Chair, 2004-2007)

American Association for Cancer Research
Program Committee 2002-2003, 2006-2007, 2012-2013, 2014-2016, 2019-2020
Scientific Committee AACR-EORTC-NCI Symposia 2003-2006
Education Committee 2006-2007
Pancreatic Cancer Action Network-AACR Research Acceleration Network Grant Scientific Review Committee 2012-2015

Accreditation Council for Continuing Medical Education
Content Validation Advisory Group 2003

Sapporo Cancer Seminar Foundation
25th International Symposium, Organizing Committee 2005

Japanese Foundation for Cancer Research
International Symposia, Member 2007-2014

The ASCO Foundation
Translational Research Professorship Review Subcommittee 2007-2008

Alliance for Clinical Trials in Oncology
Pharmacogenomics and Population Pharmacology Committee 2011- (Chair, 2011-2021)

International Workshops on Dose Optimization Strategies for Targeted Drugs
First International Workshop on Dose Optimization Strategies for Targeted Drugs: Focus on Oncolytics (Zaandam, Netherlands), Co-Chair 2015

Optimal Cancer Care Alliance (previously Value in Cancer Care Consortium)
Co-founder, Director 2017-
Treasurer, 2017-2023
Chair, 2023-

European Society for Medical Oncology
Compliance Committee, 2019-2020
Methodology for the Development of Innovative Cancer Therapies (MDICT) 2022 Organising Committee 2021-2022

International Summits on Interventional Pharmacoeconomics
First International Summit on Interventional Pharmacoeconomics (Zoom), Co-Chair 2020

Friends of Cancer Research
Dose Optimization Initiative Working Group, 2021

Institutional Committees

Michael Reese Hospital and Medical Center
Intern Selection Committee, Department of Medicine 1987-1988
Institutional Review Board, Alternate 1988-1989
Pharmacy, Therapeutics and Antibiotic Committee 1988-1989

The University of Chicago
Chairman, Office of Research Services Faculty Advisory Committee, Biological Sciences Division 1992-1995
Executive Committee, Cancer Research Center 1992-2004
Divisional Executive Committee, Biological Sciences Division 1992-2009
Clinical Chairmen's Committee, Biological Sciences Division 1992-2007
American Cancer Society Institutional Research Grant Committee, Cancer Research Center 1994-1998
Clinical Trials Director Search Committee, Department of Health Studies 1997-1998
Co-Chair, Pharmacoepidemiology Search Committee 1998-1999
Chair, Entrepreneurs Committee, Department of Medicine 1999-2000
Radiology Search Committee, Biological Sciences Division 2000-2001
Committee on Appointments and Promotions, Biological Sciences Division 2000-2004
Chair, Clinical Research Working Group, Department of Medicine 2000-2001
Protocol Accrual Closure and Monitoring Committee, Cancer Research Center 2000-2001
Committee on Intellectual Property 2001-2004
Population Sciences Search Committee, Cancer Research Center 2001
Human Genetics Search Committee, Biological Sciences Division 2002-2003
Cancer Advisory Committee, Comprehensive Cancer Center[t] 2004-2008
Chair, Clinical Research Oversight Committee, Cancer Research Center 2004-2007
Cardiology Search Committee, Department of Medicine 2005-2006
Entrepreneurial and Translational Science Advisory Committee, Department of Medicine 2006-2007
Chair, Clinical Research Advisory Committee, Comprehensive Cancer Center[t] 2007-2022
Executive Committee, Comprehensive Cancer Center[t] 2008-
UChicago Tech Faculty Advisory Committee, 2008-2010
Chicago Innovation Initiative Working Group, 2012-2013
Research Strategy Advisory Committee, Department of Medicine 2016-2017
Finance Committee, Department of Medicine 2017-2018
Clinical Research Task Force, Department of Medicine 2017-2018
Chair, COVID-19 Advisory Committee, Department of Medicine 2020-2023
Institutional Review Board, 2020-

The University of Chicago Medicine
Risk Management and Patient Safety Executive Committee, 2013-

Service to Other Institutions

Georgetown University
External Scientific Advisory Committee, Lombardi Cancer Center 2002-2011

St. Jude Children's Research Hospital
External Advisory Board, Cancer Center 2005-2018

The First People's Hospital Affiliated Shanghai Jiangtong University
External Scientific Advisor in Pharmacogenetics, The Shanghai Transplantation Research Center 2008, 2018-2019

Thomas Jefferson University
External Scientific Advisory Committee, Kimmel Cancer Center 2009-2013

Radboud University
Scientific Advisory Board, EuroTARGET 2011-2016

Dartmouth University
External Scientific Advisory Board, Norris Cotton Cancer Center 2013-2024

University of Texas Southwestern
External Advisory Board, Kidney SPORE 2014-

U-PGx Consortium
Chair, Scientific Advisory Board 2016-2022

National University Cancer Centre Singapore
Scientific Advisory Board 2016

University of Kentucky
External Scientific Advisory Board, Markey Cancer Center 2018-

Regional Committees

1987-1992 New Agents Committee, Illinois Cancer Council
1987-1992 Biological Response Modifiers Committee, Illinois Cancer Council
1989-1992 Chemoprevention Committee, Illinois Cancer Council
1990-1991 Illinois Division Research Committee, American Cancer Society

Certification

1981 Diplomate, National Board of Medical Examiners
1983 Licensed Physician and Surgeon, State of Illinois
1983 Diplomate, American Board of Internal Medicine
1985 Diplomate, Medical Oncology, American Board of Internal Medicine
1986 Diplomate, Hematology, American Board of Internal Medicine
1993 Diplomate, American Board of Clinical Pharmacology
2014- Maintenance of Certification, Internal Medicine, Medical Oncology, and Hematology, American Board of Internal Medicine
2023 Licensed Physician and Surgeon, State of Indiana

Professional Membership

1983- American College of Physicians (Fellow, 1990)
1986- American Society of Clinical Oncology (Fellow, 2007)
1987- American Society for Clinical Pharmacology and Therapeutics
1988- American Association for Cancer Research
1988- American Society of Hematology
1990- Central Society for Clinical Research
1992- European Society for Medical Oncology
2007- Association of American Physicians
2011- American College of Clinical Pharmacology (Honorary Fellow, 2011)

Honors and Awards

1975 Dreyfus Fellowship, Harvard University, Department of Biochemistry
1985 Central Society for Clinical Research, Trainee Award
1993 Unit Award, Pharmaceutical Research and Manufacturers of America Foundation
1994- Listed in The Best Doctors in America (Woodward/White)
1997- Listed in Chicago's Top Doctors, Chicago
1999 Honorary Visiting Expert, Ministry of Health, Singapore
1999- Listed in America's Top Doctors (Castle Connolly)
2001 Distinguished Lecturer, Cancer Institute of New Jersey
2002- Listed in Top Doctors: Chicago Metro Area (Castle Connolly)
2002- Leon O. Jacobson Professorship, The University of Chicago
2004 Top Membership Recruiter, American Society for Clinical Pharmacology and Therapeutics
2005- Listed in America's Top Doctors for Cancer (Castle Connolly)
2005 Special Recognition Award, National Cancer Institute
2006 Chair, 60th Annual Senior Scientific Session, The University of Chicago
2007 Elected to Association of American Physicians
2007 Fellow, American Society of Clinical Oncology
2008 Emil J. Freireich Award for Clinical Research, MD Anderson Cancer Center
2008 Institute for Pharmacogenomics and Individualized Therapy Clinical Service Award, The University of North Carolina at Chapel Hill
2009 Director's Service Award, National Cancer Institute
2009 Research Achievement Award in Clinical Pharmacology and Translational Research, American Association of Pharmaceutical Scientists
2010 Rawls-Palmer Progress in Medicine Award, American Society for Clinical Pharmacology and Therapeutics
2010 Henry T. Lynch Lectureship in Medical Genetics, NorthShore University Health System
2011 Robert Hart Waldman, M.D., Lecture, The University of Nebraska Medical Center
2011 Translational Research Professorship, American Society of Clinical Oncology
2011 Certificate of Appreciation, Japanese Society of Medical Oncology
2011 Honorary Fellow, American College of Clinical Pharmacology
2012 Visiting Professor, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Clinical Pharmacology
2012 Special Recognition, Department of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy, University of Utah
2013 Spotlight on Science Featured Speaker, American Society of Health System Pharmacists
2014 Keynote Speaker, University of Illinois College of Medicine Research Symposium
2014 Keynote Speaker, Hospital Pharmacy Europe Live
2014 Keynote Speaker, Emory University Phase I Unit Five Year Celebration
2015 Award in Excellence in Clinical Pharmacology, Pharmaceutical Research and Manufacturers of America Foundation

2016	Nominee (Scientific Advances), Giants of Cancer Care, OncLive
2019	Gruber Lectureship, Thomas Jefferson University
2020	Arthur H. Rubenstein Mentorship in Academic Medicine Award, Department of Medicine, The University of Chicago
2023	Keynote Speaker, Cancer Drug Development Forum Dose Optimization Workshop

Significant Editorial Responsibilities

1990-2003	Cancer Chemotherapy and Pharmacology, Editorial Board
1994-1996	Clinical Cancer Research, Editorial Board
1995-2016	Investigational New Drugs, Editorial Advisory Board
1996-2002	Clinical Cancer Research, Associate Editor
1999-2001	Clinical Pharmacology and Therapeutics, Editorial Advisory Committee
1999	Classic Papers and Current Comments: Clinical Pharmacology, Guest Editor
2001-2007	Journal of Clinical Oncology, Associate Editor
2001-2004	Current Pharmacogenomics, Editor-in-Chief
2001-2008	Clinical Pharmacology and Therapeutics, Editorial Board
2003-	**Clinical Advances in Hematology & Oncology, Section Editor in Oncology**
2003-2009	Clinical Cancer Research, Editorial Board
2005-2020	Pharmacogenetics and Genomics, Co-Editor-in-Chief
2012-	**Clinical Cancer Research, Editorial Board**
2021-2023	Journal of Clinical Pharmacology, Editorial Board

Patents

1998	Camptothecin drug combinations and methods with reduced side effects (inventors Mark J. Ratain & Elora Gupta), United States Patent No.: 5,786,344 (7/28/1998)
2002	Methods for detection of promoter polymorphism in a UGT gene promoter (inventors Anna Di Rienzo, Lalitha Iyer & Mark J. Ratain), United States Patent No.: 6,395,481 (5/28/2002)
2002	Methods for detection of promoter polymorphism in a UGT gene promoter (inventors Anna Di Rienzo, Lalitha Iyer & Mark J. Ratain), United States Patent No.: 6,472,157 (10/29/2002)
2004	Campothecin drug combination and methods with reduced side effects (inventors Mark J. Ratain & Elora Gupta), European Patent No.: 0768895 (9/22/2004)
2008	Methods and compositions for predicting irinotecan toxicity (inventors Mark J. Ratain, Federico Innocenti, Anna Di Rienzo & Carrie Grimsley), European Patent No.: 1629111 (5/28/2008)
2010	Methods for predicting irinotecan toxicity (inventors Mark J. Ratain, Federico Innocenti, Anna Di Rienzo & Carrie Grimsley), United States Patent No.: 7,807,350 (10/5/2010)
2014	Method for identification of sensitivity of a patient to telomerase inhibition therapy (inventors Calvin B. Harley, Laurence Elias, Jennifer Smith, Mark J. Ratain, Fabio Benedetti), United States Patent No.: 8,877,723 (11/4/2014)
2017	Method for identification of sensitivity of a patient to telomerase inhibition therapy (inventors Calvin B. Harley, Laurence Elias, Jennifer Smith, Mark J. Ratain, Fabio Benedetti), United States Patent No.: 9,617,583 (4/11/2017)

Original Research Articles

1. Ratain MJ, Golomb HM, Vardiman JW, Vokes EE, Jacobs RH, Daly K. Treatment of hairy cell leukemia with recombinant alpha-2-interferon. Blood 65, 644-648 (1985).
2. Bardawil RG, Groves C, Ratain MJ, Golomb HM, Vardiman JW. Changes in peripheral blood and bone marrow specimens following therapy with recombinant alpha$_2$ interferon for hairy cell leukemia. Am J Clin Path 85, 194-201 (1986).
3. Golomb HM, Jacobs A, Fefer A, Ozer H, Thompson J, Portlock C, Ratain M, Golde D, Vardiman J, Burke J, Brady J, Bonnem E, Spiegel R. Alpha-2 interferon therapy of hairy cell leukemia: A multicenter study of 64 patients. J Clin Oncol 4, 900-905 (1986).
4. Schilsky RL, O'Laughlin K, Ratain MJ. Phase I clinical and pharmacological study of thymidine (NSC 21548) and cis-diamminedichloroplatinum (II) in patients with advanced cancer. Cancer Res 46, 4184-4188 (1986).
5. Ratain MJ, Vogelzang NJ. Phase I and pharmacological study of vinblastine by prolonged continuous infusion. Cancer Res 46, 4827-4830 (1986).
6. Bennett CL, Vogelzang NJ, Ratain MJ, Reich S. Hyponatremia and other toxic effects during a phase I trial of recombinant human gamma interferon and vinblastine. Cancer Treat Rep 70, 1081-1084 (1986).
7. Ratain MJ, Vogelzang NJ, Sinkule JA. Interpatient and intrapatient variability in vinblastine pharmacokinetics. Clin Pharmacol Ther 41, 61-67 (1987).
8. Ratain MJ, Golomb HM, Bardawil RG, Vardiman JW, Westbrook CA, Kaminer LS, Lembersky BC, Bitter MA, Daly K. Durability of responses to interferon alfa-2b in advanced hairy cell leukemia. Blood 69, 872-877 (1987).
9. Vokes EE, Bitter MA, Ratain MJ, Prystowsky MB, Daly K, Golomb HM. Flow cytometry in hairy cell leukemia before and during interferon alfa-2b therapy. Cancer 59, 1987-1991 (1987).
10. Ratain MJ, Vogelzang NJ. Limited sampling model for vinblastine pharmacokinetics. Cancer Treat Rep 71, 935-939 (1987).
11. Ratain MJ, Kaminer LS, Bitran JD, Larson RA, LeBeau MM, Skosey C, Purl S, Hoffman PC, Wade J, Vardiman JW, Daly K, Rowley JD, Golomb HM. Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small cell carcinoma of the lung. Blood 70, 1412-1417 (1987).
12. Vogelzang NJ, Ruane M, Ratain MJ, Dhowlatshahi K, Chodak GW. A programmable and implantable pumping system for systemic chemotherapy: A performance analysis in 52 patients. J Clin Oncol 5, 1968-1976 (1987).
13. Lembersky BC, Ratain MJ, Westbrook C, Golomb HM. Rapid response to 2'deoxycoformycin in advanced hairy cell leukemia after failure of interferons alpha and gamma. Amer J Hematol 27, 60-62 (1988).
14. Golomb HM, Ratain MJ, Fefer A, Thompson J, Golde DW, Ozer H, Portlock C, Silber R, Rappeport J, Bonnem E, Spiegel R, Tensen L, Burke JS, Vardiman JW. Randomized study of the duration of treatment with interferon alfa-2b in patients with hairy cell leukemia. J Natl Cancer Inst 80, 369-373 (1988).
15. Vardiman JW, Gilewski TA, Ratain MJ, Bitter MA, Bradlow BA, Golomb HM. Evaluation of Leu M-5 (CD11c) in hairy cell leukemia by the alkaline phosphatase anti-alkaline phosphatase technique. Am J Clin Path 90, 250-256 (1988).
16. Lembersky BC, Ratain MJ, Golomb HM. Skeletal complications in hairy cell leukemia: diagnosis and therapy. J Clin Oncol 6, 1280-1284 (1988).

17. Ratain MJ, Staubus AE, Schilsky RL, Malspeis L. Limited sampling models for amonafide (NSC 308847) pharmacokinetics. Cancer Res 48, 4127-4130 (1988).

18. Ackland SP, Choi KE, Ratain MJ, Egorin MJ, Williams SF, Sinkule JA, Bitran JD. Human plasma pharmacokinetics of thiotepa following administration of high-dose thiotepa and cyclophosphamide. J Clin Oncol 6, 1192-1196 (1988).

19. Ratain MJ, Vardiman JW, Barker CM, Golomb HM. Prognostic variables in hairy cell leukemia after splenectomy as initial therapy. Cancer 62, 2420-2424 (1988).

20. Ratain MJ, Golomb HM, Vardiman JW, Westbrook CA, Barker C, Hooberman A, Bitter MA, Daly K. Relapse after interferon alfa-2b therapy for hairy-cell leukemia: Analysis of prognostic variables. J Clin Oncol 6, 1714-1721 (1988).

21. Ratain MJ, Schilsky RL, Wojack BR, Simon T, Senekjian E, Vogelzang NJ. Hydroxyurea and etoposide: In vitro synergy and phase I clinical trial. J Natl Cancer Inst 80, 1412-1416 (1988).

22. Ackland SP, Ratain MJ, Vogelzang NJ, Choi KE, Ruane M, Sinkule JA. Pharmacokinetics and pharmacodynamics of long-term continuous-infusion doxorubicin. Clin Pharmacol Ther 45, 340-347 (1989).

23. Vokes EE, Schilsky RL, Choi KE, Magid DM, Guarnieri CM, Whaling SM, Ratain MJ, Weichselbaum RR, Panje WR. A randomized study of inpatient versus outpatient continuous infusion chemotherapy for patients with locally advanced head and neck cancer. Cancer 63, 30-36 (1989).

24. Ratain MJ, Schilsky RL, Choi KE, Guarnieri C, Grimmer D, Vogelzang NJ, Senekjian E, Liebner MA. Adaptive control of etoposide dosing: Impact of interpatient pharmacodynamic variability. Clin Pharmacol Ther 45, 226-233 (1989).

25. Choi KE, Ratain MJ, Williams SF, Golick JA, Beschorner JC, Fullem L, Bitran JD. Plasma pharmacokinetics of high-dose oral melphalan in patients treated with trialkylator chemotherapy and autologous bone marrow reinfusion. Cancer Res 49, 1318-1321 (1989).

26. Egorin MJ, Forrest A, Belani CP, Ratain MJ, Abrams JS, Van Echo DA. A limited sampling strategy for cyclophosphamide pharmacokinetics. Cancer Res 49, 3129-3133 (1989).

27. Moormeier J, Ratain MJ, Vardiman JW, Daly K, Golomb HM. Low dose interferon in hairy cell leukemia. J Natl Cancer Inst 81, 1172-1174 (1989).

28. Moormeier J, Westbrook CA, Ratain MJ, Golomb HM. Interferon alfa-2B antibodies and clinical resistance in a patient with hairy cell leukemia. Leukemia Lymphoma 1, 43-45 (1989).

29. Johnston C, Senekjian EK, Ratain MJ, Talerman A. Conservative management of primary cervical lymphoma using combination chemotherapy: a case report. Gynecol Oncol 35, 391-394 (1989).

30. Schilsky RL, Ratain MJ. Clinical pharmacokinetics of high dose leucovorin after intravenous and oral administration. J Natl Cancer Inst 82, 1411-1415 (1990).

31. Richards JM, Mick R, Latta JM, Daly K, Ratain MJ, Vardiman JW, Golomb HM. Serum soluble IL-2 receptor is associated with clinical and pathologic disease status in hairy cell leukemia. Blood 76, 1941-1945 (1990).

32. Ratain MJ, Robert J, van der Vijgh WJF. Limited sampling models for doxorubicin pharmacokinetics. J Clin Oncol 9, 871-876 (1991).

33. Vokes EE, Ratain MJ, Janisch L, Hoffman PC, Golomb HM, Schilsky RL. A phase I study of cisplatin, 5-fluorouracil and leucovorin with escalating doses of hydroxyurea in chemotherapy naive patients. Eur J Cancer 27, 217-218 (1991).

34. Golomb HM, Fefer A, Golde DW, Ozer H, Portlock C, Silber R, Rappeport J, Ratain MJ, Thompson J, Bonnem E, Spiegel R, Tensen L, Burke JS, Vardiman JW. Survival experience of 195 patients with hairy cell leukemia treated in a multi-institutional study with interferon-alfa 2b. Leukemia Lymphoma 4, 99-102 (1991).

35. Vokes EE, Raschko JW, Vogelzang NJ, Warfield EE, Ratain MJ, Doroshow JH, Schilsky RL. Five day infusion fluorodeoxyuridine with high dose oral leucovorin: A phase I study. Cancer Chemother Pharmacol 28, 69-73 (1991).

36. Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F. Pharmacologically-based dosing of etoposide: A means of safely increasing dose-intensity. J Clin Oncol 9, 1480-1486 (1991).

37. Golomb HM, Ratain MJ, Fefer A, Thompson J, Portlock CS, Ozer H, Mick R, Chiavello J, Israel RJ, Bonnem EM. Low dose interferon alfa-2B for the induction of remission of hairy cell leukemia: A multi-institutional study of 49 patients. Leukemia Lymphoma 5, 335-340 (1991).

38. Platanias LC, Miller CB, Mick R, Hart RD, Ozer H, McEvilly JM, Jones RJ, Ratain MJ. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer patients. J Clin Oncol 9, 2021-2026 (1991).

39. Ratain MJ, Mick R, Berezin F, Janisch L, Schilsky RL, Williams SF, Smiddy J. Paradoxical relationship between acetylator phenotype and amonafide toxicity. Clin Pharmacol Ther 50, 573-579 (1991).

40. Mick R, Ratain MJ. Modeling interpatient pharmacodynamic variability of etoposide. J Natl Cancer Inst 83, 1560-1564 (1991).

41. Vokes EE, Moormeier JA, Ratain MJ, Egorin MJ, Haraf DJ, Mick R, Weichselbaum RR. 5-fluorouracil, hydroxyurea, and escalating doses of continuous infusion cisplatin with concomitant radiotherapy: A clinical and pharmacologic study. Cancer Chemother Pharmacol 29, 178-184 (1992).

42. Miller CB, Platanias LC, Mills SR, Zahurak ML, Ratain MJ, Ettinger DS, Jones RJ. A phase I/II trial of erythropoietin in the treatment of cisplatin-associated anemia. J Natl Cancer Inst 84, 98-103 (1992).

43. Kodish E, Stocking C, Ratain MJ, Kohrman A, Siegler M. Ethical issues in phase I oncology research: A comparison of investigators and IRB chairpersons. J Clin Oncol 10, 1810-1816 (1992).

44. Golomb HM, Ratain MJ, Mick R, Daly K. Interferon treatment for hairy cell leukemia; an update on a cohort of 69 patients treated from 1983-86. Leukemia 6,1177-1180 (1992).

45. Schilsky RL, Ratain MJ, Janisch L, Vogelzang NJ, Lucas VS, Ravitch J, Hohneker JA, Clendeninn NJ, Tuttle RL. Phase I clinical and pharmacologic study of 502U83 administered as a 24 hour continuous intravenous infusion. Cancer Chemother Pharmacol 31, 283-288 (1993).

46. Vokes EE, Ratain MJ, Mick R, McEvilly JM, Haraf D, Hamasaki V, Kozloff M, Weichselbaum RR, Panje WR, Wenig B, Berezin F. Cisplatin, 5-fluorouracil and leucovorin augmented by interferon alfa-2b in head and neck cancer: a clinical and pharmacologic analysis. J Clin Oncol 11, 360-368 (1993).

47. Mick R, Ratain MJ. Model-guided determination of maximal tolerated dose in phase I clinical trials: Evidence for increased precision. J Natl Cancer Inst 85, 217-223 (1993).

48. Ratain MJ, Priest E, Janisch L, Vogelzang NJ. Phase I study of subcutaneous recombinant interleukin-2 and interferon alfa-2a. Cancer 71, 2371-2376 (1993).

49. Schilsky RL, Janisch L, Berezin F, Mick R, Vogelzang NJ, Ratain MJ. Phase I clinical and pharmacological study of iododeoxyuridine and bleomycin in patients with advanced cancer. Cancer Res 53, 1293-1296 (1993).

50. Ratain MJ, Mick R, Berezin F, Janisch L, Schilsky RL, Vogelzang NJ, Lane LB. Phase I study of amonafide dosing based on acetylator phenotype. Cancer Res 53, 2304-2308 (1993).

51. Vokes EE, Dolan ME, Krishnasamy S, Mick R, Ratain MJ, Berezin F, Brachman D, Whitman G, Schilsky RL, Weichselbaum RR, Charette J, Dohrmann GJ, Hekmatpanah J. 5-fluorouracil, hydroxyurea and escalating doses of iododeoxyuridine with concomitant radiotherapy for malignant gliomas: a clinical and pharmacologic analysis. Ann Oncol 4, 591-595 (1993).

52. Vokes EE, O'Brien S, Vogelzang NJ, Schilsky RL, Ratain MJ. Five day infusional fluorodeoxyuridine with oral leucovorin and escalating doses of interferon alfa-2b: a phase I study. Cancer Chemother Pharmacol 32, 347-352 (1993).

53. Lichtman SM, Ratain MJ, Van Echo DA, Rosner G, Egorin MJ, Budman DR, Norton L, Vogelzang NJ, Schilsky RL. Phase I trial of granulocyte-macrophage colony stimulating factor plus high-dose cyclophosphamide given every 2 weeks: a Cancer and Leukemia Group B study. J Natl Cancer Inst 85, 1319-1326 (1993).

54. Samuels BL, Mick R, Vogelzang NJ, Williams SF, Schilsky RL, Safa AR, O'Brien S, Ratain MJ. Modulation of vinblastine resistance with cyclosporine A: a phase I study. Clin Pharmacol Ther 54, 421-429 (1993).

55. Vogelzang NJ, Mick R, Janisch L, Berezin F, Schilsky RL, Ratain MJ. A phase I and pharmacokinetic study of a new antineoplastic agent: pyrazine diazohydroxide (NSC 361456). Cancer Res 54, 114-119 (1994).

56. Devine SM, Ratain MJ, Janisch L, Richards JM, Williams SF, Schilsky RL, Vogelzang NJ, Skosey C. Phase I trial of thiotepa, granulocyte-macrophage colony stimulating factor and prednisone or pentoxifylline in patients with refractory solid tumors. Oncol Rep 1, 213-216 (1994).

57. Platanias LC, Ratain MJ, O'Brien S, Larson RA, Vardiman JW, Shaw JP, Williams SF, Baron JM, Parker K, Woodworth TG. Phase I trial of a genetically engineered interleukin-2 fusion toxin (DAB_{486} IL-2) as a 6 hour intravenous infusion in patients with hematologic malignancies. Leukemia Lymphoma 14, 257-262 (1994).

58. Fleming GF, Ratain MJ, O'Brien SM, Schilsky RL, Hoffman PC, Richards JM, Vogelzang NJ, Kasunic DA, Earhart RH. Phase I study of adozelesin administered by 24-hour continuous intravenous infusion. J Natl Cancer Inst 86, 368-372 (1994).

59. Mick R, Ratain MJ. Bootstrap validation of pharmacodynamic models defined by way of stepwise linear regression. Clin Pharmacol Ther 56, 217-222 (1994).

60. Kobayashi K, Vogelzang NJ, O'Brien SM, Schilsky RL, Vokes EE, Ratain MJ. A phase I study of intermittent infusion cladribine in patients with solid tumors. Cancer 74, 168-173 (1994).

61. Mitchell RB, Dolan ME, Janisch L, Vogelzang NJ, Ratain MJ, Schilsky RL. Sequential therapy with dacarbazine and carmustine: A phase I study. Cancer Chemother Pharmacol 34, 509-514 (1994).

62. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan (CPT-11) in humans: correlation of glucuronidation with diarrhea. Cancer Res 54, 3723-3725 (1994).

63. Janisch L, Mick R, Schilsky RL, Vogelzang NJ, O'Brien S, Kut M, Ratain MJ. Prognostic factors for survival in patients treated on phase I clinical trials. Cancer 74, 1965-1973 (1994).

64. Mick R, Lane N, Daugherty C, Ratain MJ. Physician-determined patient risk of toxicity: impact on enrollment and decision making in phase I cancer trials. J Natl Cancer Inst 86, 1685-1693 (1994).

65. Karlsson MO, Port RE, Ratain MJ, Sheiner LB. A population model for the leukopenic effect of etoposide. Clin Pharmacol Ther 57, 325-334 (1995).

66. Ratain MJ, Rosner G, Allen SL, Costanza ME, Van Echo DA, Henderson IC, Schilsky RL. Population pharmacodynamic study of amonafide: A Cancer and Leukemia Group B study. J Clin Oncol 13, 741-747 (1995).

67. Larson RA, Geller RB, Janisch L, Suarez D, Milton J, Grochow LB, Ratain MJ. Encephalopathy is the dose-limiting toxicity of intravenous hepsulfam: results of a phase I trial in patients with advanced hematological malignancies. Cancer Chemother Pharmacol 36, 204-210 (1995).

68. Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, Siegler M. Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 13, 1062-1072 (1995).

69. Costanza ME, Berry D, Henderson IC, Ratain MJ, Wu K, Shapiro C, Duggan D, Kalra J, Berkowitz I, Lyss AP. Amonafide: an active agent in the treatment of previously untreated advanced breast cancer: a Cancer and Leukemia Group B study (CALGB 8642). Clin Cancer Res 1, 699-704 (1995).

70. Lilenbaum RC, Ratain MJ, Miller AA, Hargis JB, Hollis DR, Rosner GL, O'Brien SM, Brewster L, Graham L, Green MR, Schilsky RL. Phase I study of paclitaxel and topotecan in patients with advanced tumors: a Cancer and Leukemia Group B study. J Clin Oncol 13, 2230-2237 (1995).

71. Kobayashi K, Vokes EE, Vogelzang NJ, Janisch L, Soliven B, Ratain MJ. A phase I study of suramin (NSC 34936) given by intermittent infusion without adaptive control in patients with advanced cancer. J Clin Oncol 13, 2196-2207 (1995).

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