

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
U.S. Patent No. 11,344,552

**DECLARATION OF PAUL E. OBERSTEIN, M.D.,
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 11,344,552**

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I, Paul E. Oberstein, declare as follows:

I. INTRODUCTION

1. I have been retained by Patent Owner Ipsen Biopharm Ltd. (“Ipsen”) as an independent technical expert in this proceeding before the United States Patent and Trademark Office (“PTO”) Patent Trial and Appeal Board (“Board”) regarding U.S. Patent No. 11,344,552 (the “’552 Patent”).

2. I understand that CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, “CSPC” or “Petitioners”) filed a petition for *Inter Partes* Review (“IPR”) against claims 1-15 of the ’552 Patent (“the Challenged Claims”), which includes the Declaration of Dr. Mark Ratain (“Ratain Declaration” or “Ratain Decl.”) (Ex. 1002).

3. I have been asked by counsel for Patent Owner to analyze and explain why I disagree with certain opinions set forth in the Ratain Declaration.

4. I am being compensated at my customary consulting rate of \$850/hour for the time I spend on this matter. My compensation is in no way contingent on the substance of my opinions and testimony or the outcome of this or any other proceeding. I have no other interest in this proceeding.

II. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

5. My qualifications and professional experience, including a list of my publications and my expertise and professional activities, are described in my

curriculum vitae, a copy of which is provided as Appendix A. The following is a summary of my qualifications and professional experience.

6. I am a board-certified medical oncologist focused in gastrointestinal (“GI”) tract cancers, especially colorectal, pancreatic, and gastric cancers. I currently serve as the Service Chief in the GI Oncology practice within the Perlmutter Cancer Center at NYU Langone Health. In this role, I have primary oversight of 10 physicians and patient care teams in Manhattan, Brooklyn, and Long Island. Our GI Oncology group sees over 1,500 new, unique patients per year and has over 350 patient encounters a week. On a weekly basis, I see 70-80 patients, and about one-half of my patients have pancreatic cancer. In addition to seeing patients, I oversee weekly meetings with multidisciplinary teams, including medical oncology, radiation oncology, palliative care, social work, nutrition, and research to provide group oversight. In this role, I have prescribed and overseen numerous chemotherapy regimens for the treatment of pancreatic cancer, including: gemcitabine/nab-paclitaxel formulations; FOLFIRINOX, and modifications to same; and NALIRIFOX.

7. I am also the co-Director of the Pancreas Disease Center at NYU Langone Health and an Associate Professor in the Department of Medicine at NYU Langone Health. I was formerly Director of GI Oncology at the Perlmutter Cancer

Center at NYU Langone Health and Assistant/Interim Director of the Pancreatic Cancer Center at the Perlmutter Cancer Center at NYU Langone Health.

8. Since my recruitment to NYU, I have served as the co-leader for the GI Disease Management Group at the Perlmutter Cancer Center at NYU Langone Health. In this role, I have primary responsibility for all clinical trials involving GI cancers at NYU Langone Health. In this role, I oversee a team consisting of regulatory and data specialists, clinical research coordinators and research nurses. I oversee a weekly meeting in which we review all prospective and active studies in this group, as well as review individual patients enrolled in clinical studies. We currently have a portfolio of over 40 clinical studies and in 2024 enrolled over 80 unique patients on interventional clinical studies.

9. I received my M.D. from The Ohio State University in 2006. After receiving my medical degree in 2006, I completed a residency in Internal Medicine at Temple University Hospital in Philadelphia, PA. I then pursued a fellowship in Hematology and Oncology for three years at Columbia University in New York, followed by a two-year fellowship in Patient Oriented Research at Columbia University.

10. I became board certified in Internal Medicine in 2009 and in Medical Oncology in 2014. Then, in 2015, I obtained my Masters in Biostatistics from

Columbia University, where I focused on issues related to clinical and translational investigation and the design and statistical analysis of clinical studies.

11. My research activities have focused on designing and conducting clinical trials using novel agents including immunotherapies for the treatment of colorectal, pancreatic, and other GI cancer patients. I am particularly interested in building collaborative teams to design and implement novel translational clinical trials in colorectal, pancreatic, and other GI cancers, and improving care delivery and multi-disciplinary collaborative care for GI cancer patients.

12. I have served as a principal investigator or site principal investigator on more than 20 multi-center clinical studies, including investigator-initiated studies and studies involving the FOLFIRINOX regimen, and modifications thereof. Currently, I am the site principal investigator on multiple active clinical studies including studies in metastatic pancreatic cancer patients, including a recently completed trial (NCT04229004) evaluating the FOLFIRINOX regimen. I have received more than \$4.5 million in funding from various pharmaceutical companies related to my research activities.

13. I am also a member of the Protocol Review and Monitoring Committee (“PRMC”) in the Perlmutter Cancer Center at NYU Langone Health. The PRMC is tasked with reviewing the detailed plans and protocols for proposed clinical studies to evaluate their scientific quality and validity, among other things. If the PRMC

approves the proposed clinical study, the clinical study protocol is sent to the Institutional Review Board (“IRB”) for review. The IRB assesses the safety, efficacy, benefits, adverse reactions, and outcomes of proposed clinical studies with the primary goal of ensuring patient safety. There is a scientific review committee at every comprehensive cancer center that conducts clinical research, and typically, the scientific review committee reviews all proposed clinical studies before they go to the facility’s IRB for approval.

14. In addition, I have also been involved in developing the curriculum for the Graduate Medical Education Program at NYU Langone Health. For example, in 2019, I received the Cancer Clinical Investigator Team Leadership Award from the National Cancer Institute, which provided funding to design and implement a lecture series in clinical investigation. The lecture series I designed and implemented focused on clinical and translational research covering the topics of trial design, basic biostatistics, regulatory considerations, and practical applications of clinical research.

15. Additionally, in 2019, I developed a new didactic course for the fellowship program to provide a comprehensive course in all aspects of GI cancers. In developing this course, I recruited faculty members for participation, designed the curriculum, and led lectures covering topics related to GI cancers, including pathology, genetics, and translational research. I have also led various peer-lectures

and talks, including on colorectal cancer immunology and topics relating to pancreatic cancer. Additionally, throughout my career I have dedicated a portion of my time to mentoring and advising predoctoral and postdoctoral students and oncology faculty.

16. Before joining NYU Langone Health in 2018, I held appointments as an Assistant Attending Physician at New York Presbyterian Hospital and Assistant Professor in the Department of Medicine at Columbia University. From 2014 to 2018, I also served as a member on the Protocol Review and Monitoring Committee for the Herbert Irving Comprehensive Cancer Center at Columbia University. Similar to the PRMC that I serve on currently, the Protocol Review and Monitoring Committee at Columbia University is tasked with reviewing proposed clinical studies for their scientific validity and merit before the clinical study protocol is reviewed by the IRB.

17. I have published more than 30 peer-reviewed papers and have presented more than 25 oral and poster presentations regarding GI cancers, including the use of the FOLFIRINOX regimen and modifications thereto. I have also sat on several advisory boards and served as a peer reviewer for journals in the past, including the Journal of Clinical Oncology, JAMA, and Clinical Cancer Research.

III. MATERIALS CONSIDERED

18. The opinions contained in this Declaration are based on the documents I reviewed, as well as my education, years of professional experience, and knowledge. In forming my opinions expressed in this Declaration, I have reviewed the following documents and other materials cited herein in this Declaration:

- Petition for *Inter Partes* Review of the '552 Patent ("Petition") (Paper 1);
- Petitioner's exhibits filed with the Petition, including both Ratain Declarations (*see* Ex. 1001-1123, Ex. 1200-1207);
- Patent Owner's exhibits filed with the Patent Owner's Preliminary Response (*see* Ex. 2001-2035);
- The Board's Decision Granting Institution of *Inter Partes* Review ("Institution Decision") (Paper 13);
- Patent Owner's exhibits filed with the Patent Owner's Response:

Exhibit	Short Name	Description
2036	March 2015 NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma Version 2.2015
2037	Ratain 2009	M.J. Ratain et al., <i>Optimising the design of phase II oncology trials: the importance of randomisation</i> , Eur. J. Cancer, 2009 Jan;45(2):275-80 (2009)
2038	Ychou	M. Ychou, et al., <i>An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors</i> , Ann. Oncol., 14(3):481-89 (2003)

2039	Gourgou-Bourgade	S. Gourgou-Bourgade et al. <i>Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial</i> , J. Clin. Oncol., 31, 23-29 (2013)
2040	FDA Approval Letter	FDA Supplemental Approval Letter for the new indication of Onivyde® in combination with oxaliplatin, fluorouracil and leucovorin, for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma, dated February 13, 2024
2041	Oh	S.Y. Oh et al., <i>Pilot study of irinotecan/oxaliplatin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil-refractory pancreatic cancer</i> , Invest. New Drugs, 2010 Jun;28(3):343-49 (2010)
2042	Zhang	H. Zhang et al., <i>Oxaliplatin plus irinotecan vs irinotecan as second-line treatment in pancreatic cancer patients: a randomized-controlled open-label Phase II study</i> , Gastroenterol. Rep., 2023 Feb 3;11:goac088 (2023)
2043	Gunturu	K.S. Gunturu, et al., <i>FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity</i> , Med. Oncol. 2013 Mar;30(1):361 (2013)
2044	Amiri-Kordestani	L. Amiri-Kordestani, et al., <i>Why do phase III clinical trials in oncology fail so often?</i> , J. Natl. Cancer Inst., 2012 Apr 18;104(8):568-9 (2012)
2045	Booth	B. Booth, et al., <i>Oncology's trials</i> , Nat. Rev. Drug Disc. 2(8):609-10 (2003)
2046	Vasile	E. Vasile, et al., <i>Neoadjuvant Modified Folfoxiri in Locally advanced Pancreatic Cancer</i> , Ann. Oncol., 23:ix241 (2012)
2047	James	E.S. James et al., <i>Interim analysis of a phase II study of dose-modified FOLFIRINOX (mFOLFIRINOX) in</i>

		<i>locally advanced (LAPC) and metastatic pancreatic cancer (MPC), J. Clin. Oncol. 32, 256-256 (2014)</i>
2048	Stein	<i>S.M. Stein et al., Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer, Br. J. Cancer, 2016 Mar 29;114(7):737-43 (2016)</i>
2049	Yoshida	<i>K. Yoshida et al., A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer, Oncotarget. 2017 Nov 30;8(67):111346-111355 (2017)</i>
2050	Li	<i>X. Li et al., Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population, Cancer Lett. 2017 Oct 10;406:22-26 (2017)</i>
2051	Ozaka	<i>M. Ozaka et al., A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer, Cancer Chemother. Pharmacol. 2018 Jun;81(6):1017-1023 (2018)</i>
2052	Wang	<i>Z.Q. Wang et al., The efficacy and safety of modified FOLFIRINOX as first-line chemotherapy for Chinese patients with metastatic pancreatic cancer, Cancer Commun. (Lond). 2019 May 8;39(1):26 (2019)</i>
2053	Ramanathan	<i>R.K. Ramanathan et al., Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313, J. Clin. Oncol. 2019 May 1;37(13):1062-1069 (2019)</i>
2054	Wei	<i>T. Wei et al., Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer, Mol. Cancer Ther., 2019 Jan;18(1):196-203 (2019)</i>

2055	Vivaldi 2019	C. Vivaldi et al., <i>Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study</i> , Cancers (Basel). 2019 Jul 4;11(7):939 (2019)
2056	Peddi	P.F. Peddi et al., <i>A Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma</i> , JOP. 2012 Sep 10;13(5):497-501 (2012)
2057	Lowrey	M.A. Lowery et al., <i>Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC)</i> , J. Clin. Oncol. 30, 4057-4057 (2012)
2058	Hosein	P.J. Hosein et al., <i>A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma</i> , BMC Cancer. 2012 May 29;12:199 (2012)
2059	Ghorani	E. Ghorani et al., <i>Safety and efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: a UK single-center experience</i> , Oncology 2015; 89(5):281-7 (2015)
2060	Kaga	Y. Kaga et al., <i>Early tumor shrinkage as a predictor of favorable outcomes in patients with advanced pancreatic cancer treated with FOLFIRINOX</i> , Oncotarget, 2016; 7: 67314-67320 (2016)
2061	De Jesus	V.H.F. de Jesus et al., <i>Retrospective comparison of the efficacy and the toxicity of standard and modified FOLFIRINOX regimens in patients with metastatic pancreatic adenocarcinoma</i> , J. Gastrointest. Oncol. 2018 Aug;9(4):694-707 (2018)
2062	Kang	H. Kang et al., <i>Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic</i>

		<i>Cancer</i> , World J. Gastrointest. Oncol. 2018 Nov 15; 10(11):421-430 (2018)
2063	Yamada	Y. Yamada et al., <i>Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy</i> , <i>Cancers (Basel)</i> , 2018 Nov 16;10(11):454 (2018)
2064	Eraslan	E. Eraslan, et al., <i>First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience</i> , <i>J. Oncol. Sci.</i> , Apr. 2019 5:1 (2019)
2065	Sasaki	T. Sasaki et al., <i>Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis</i> , <i>In Vivo</i> . 2019 Jan-Feb;33(1):271-276 (2019)
2066	Vivaldi 2021	C. Vivaldi et al., <i>Comprehensive pharmacogenetic analysis of DPYD, UGT, CDA, and ABCB1 polymorphisms in pancreatic cancer patients receiving mFOLFIRINOX or gemcitabine plus nab-paclitaxel</i> , <i>Pharmacogenomics J.</i> 2021 Apr;21(2):233-242 (2021)
2067	Cavanna	L. Cavanna et al., <i>Modified FOLFIRINOX for unresectable locally advanced/metastatic pancreatic cancer. A real-world comparison of an attenuated with a full dose in a single center experience</i> , <i>Onco. Targets Ther.</i> 2019 Apr 23;12:3077-3085 (2019)
2068	Cui	H. Cui et al., <i>A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer</i> , <i>Med. Sci. Monit.</i> 2020 Oct 26;26:e927654 (2020)
2069	Pacheco-Barcia	V. Pacheco-Barcia et al., <i>A systemic inflammation response index (SIRI) correlates with survival and predicts oncological outcome for mFOLFIRINOX therapy in metastatic pancreatic cancer</i> , <i>Pancreatology</i> 2020 Mar;20(2):254-264 (2020)

2070	Takeda	T. Takeda et al., <i>Improved prognosis of pancreatic cancer patients with peritoneal metastasis</i> , Pancreatology 2021 Aug;21(5):903-911 (2021)
2071	Zhou	Y. Zhou et al., <i>Delta HU is a potential marker to predict chemotherapy response for unresectable pancreatic ductal adenocarcinoma</i> , Pancreatology 2021 Jun;21(4):763-770 (2021)
2072	Oberstein	P.E. Oberstein et al., <i>Pancreatic cancer: why is it so hard to treat?</i> , Therap. Adv. Gastroenterol. 2013 Jul;6(4):321-37 (2013)
2073	Ratain Deposition	Deposition Transcript of Mark J. Ratain In the Matter of CSPC Pharma vs. Ipsen Biopharm, dated October 24, 2025
2074	Camptosar 2014 Label	Label for CAMPTOSAR® (Irinotecan) Injection, intravenous infusion, Revised 12/2014
2075	Knox II	J.J. Knox et al. <i>Early results of the PASS-01 trial: Pancreatic adenocarcinoma signature stratification for treatment-01</i> , J. Clin. Oncol. 42, LBA4004-LBA4004 (2024)

IV. SUMMARY OF OPINIONS

19. Counsel for Ipsen has asked me to provide my expert opinions regarding whether claims 1-15 of the '552 Patent would have been obvious to a person of ordinary skill in the art ("POSA") as of the priority date of August 21, 2015. Based on my education, training, and extensive clinical experience treating patients with metastatic pancreatic cancer, I have reviewed the materials identified

in Section III and considered the arguments presented by CSPC and Dr. Ratain in support of their obviousness contentions.

20. In my opinion, none of the challenged claims of the '552 Patent would have been obvious to a POSA. The prior art references relied upon by CSPC and Dr. Ratain do not teach or suggest the specific combination of modifications to FOLFIRINOX recited in the claims. A POSA would not have been motivated to simultaneously (1) substitute liposomal irinotecan for conventional irinotecan, (2) reduce the oxaliplatin dose from 85 mg/m² to 60 mg/m², (3) remove the 400 mg/m² 5-FU bolus, and (4) adjust the liposomal irinotecan dose to 60 mg/m²—all while maintaining therapeutic efficacy and tolerability. Even if a POSA had been motivated to pursue such modifications, the prior art provides no basis for a reasonable expectation that this specific combination would successfully treat metastatic pancreatic cancer. The claimed methods represent a significant advance in the treatment of this devastating disease, with the Phase III trial achieving improved efficacy compared to another standard of care chemotherapy (Gem/nab-paclitaxel), and indirect analysis demonstrating comparable or improved efficacy with a better safety profile compared to FOLFIRINOX. The clinical benefits demonstrated by the claimed methods were unexpected in view of the prior art and support the non-obviousness of claims 1-15.

V. LEGAL STANDARDS

21. In this section I describe my understanding of certain legal principles that I have relied upon in forming my opinions set forth in this Declaration.

22. I have been informed of these legal standards by counsel for Ipsen. I am not an attorney, and I have not researched patent law. I am relying only on Ipsen's attorneys relating to these legal standards.

A. Person of Ordinary Skill in the Art

23. I am informed that patent validity is determined from the perspective of a POSA at the time of the invention. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, conventional wisdom in the art, and is a person of ordinary creativity—not an automaton.

24. In deciding the level of ordinary skill in the art, I am informed that the following factors may be considered: the levels of education and experience of persons working in the field; the types of problems encountered in the field; and the sophistication of the technology.

B. Claim Construction

25. I am informed that a patent may include two types of claims, independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim or another dependent claim. I am informed that a dependent

claim includes all the limitations that it recites, in addition to the limitations recited in the claim from which it depends.

26. I understand that patent claim terms can be interpreted, or “construed.” I understand that, in construing a claim, the words of a patent claim are given their plain meaning, as a POSA would understand them at the time of the invention, in view of the patent and file history (which I understand is considered “intrinsic” evidence), unless their meaning is defined or disclaimed. I am informed that dictionaries, treatises, and other “extrinsic” sources of evidence may assist in determining the plain meaning of a term, but they cannot override a meaning that is otherwise unambiguous based on the intrinsic evidence.

27. I have been informed by Ipsen’s counsel that claim construction is a matter of law for the arbiter of law to decide. I am informed that, in an *inter partes* review, the Patent Trial and Appeal Board interprets claims in the same way as a district court would. Likewise, I understand that a POSA interprets claims in the same way in both types of proceedings.

28. I reserve my right to amend or alter my analysis and opinions in view of any claim constructions adopted by the arbiter of law.

C. Prior Art Status

29. I understand that the “priority date” of a patent is the date on which it is filed, or the date on which an earlier-filed patent application is filed if the patentee claims the benefit of priority to that earlier-filed patent application.

30. I understand that a U.S. or foreign patent or patent application qualifies as prior art to a patent being challenged, if the date of issuance or publication of the patent or patent application is prior to the priority date of the challenged patent.

31. I understand that a printed publication, such as an article published in a magazine or trade publication, qualifies as prior art to the challenged patent if the date of publication is prior to the priority date of the challenged patent.

D. Written Description

32. I understand that a patent must contain a written description of the product or method claimed in the patent. The issue of written description is decided on a claim-by-claim basis, not as to the entire patent or groups of claims. To satisfy the written description requirement, the patent specification must describe each and every limitation of a patent claim, in sufficient detail to disclose the claimed invention, although the exact words found in the claim need not be used. If the patent specification does not include an adequate written description of the full scope of the claim, then the claim is invalid.

33. When determining whether the specification discloses the invention, the claim must be viewed as a whole. The written description requirement is satisfied if the specification clearly allows a POSA to recognize that the inventors invented the full scope of what is claimed as of the effective filing date of the claimed invention.

34. I understand that the patent specification demonstrates possession by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, and diagrams, that fully set forth the claimed invention. Factors to consider in evaluating whether the specification has provided an adequate written description include: the nature and scope of the patent claims; the complexity, predictability, and maturity of the technology at issue; the existing knowledge in the relevant field; and the scope and content of the prior art.

E. Obviousness

35. I understand that a claimed invention is not patentable if the claimed invention would have been obvious to a POSA in the field of the invention at the time of the invention.

36. I have been informed and understand that the obviousness analysis requires evaluating the claim language as a whole, including comparing each and every limitation of the properly construed claim language to the prior art.

37. I understand that a POSA cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

38. I understand that a POSA provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

39. I understand that in order to show obviousness based on a single reference or a combination of references, a particular motivation to modify the reference or combine the teachings in the references, and a reasonable expectation of success in practicing the claimed invention, must be shown.

40. I understand that the obviousness inquiry includes consideration of various factors, such as the scope and content of the prior art, the differences between the prior art and the claims at issue, the knowledge of a POSA at the time of invention, and any objective factors indicating non-obviousness.

41. I am informed that objective factors indicating non-obviousness, also known as objective indicia, may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of the process or product covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; and

(6) deliberate copying of the invention by others. I also understand that there must be a relationship or nexus between any such objective indicia and the claimed invention.

42. I understand that a showing of unexpected results may support a conclusion of non-obviousness. I understand that unexpected results may be shown where the claimed invention exhibits properties that are much greater than would have been predicted, as compared to the closest prior art. I understand that unexpected results must be a difference in kind, not just a difference in degree. I further understand that evidence from after the patent is filed may be considered in assessing unexpected results, but the results must be unexpected by a POSA at the time of the effective filing date.

F. Burden of Proof

43. I understand that the Petition must identify with particularity the grounds on which it is challenging each claim and the evidence that supports each ground.

44. I understand that the CSPC bears the burden of showing that it is more likely than not that the challenged claims are unpatentable.

VI. BACKGROUND

45. I have been asked to review the state of the relevant art as of August 21, 2015, and to provide a background of the relevant technology of the invention.

46. I have also been asked to provide responses, where required, to Dr. Ratain's "Background and State of the Art" section.

A. Treatment of Metastatic Pancreatic Cancer Before FOLFIRINOX

47. Pancreatic cancer ranks among the primary causes of cancer mortality in the United States. The disease typically goes undetected until reaching an advanced stage because early-stage symptoms are often absent. When pancreatic cancer has metastasized, representing the disease's most severe form, treatment becomes exceptionally challenging. Metastatic pancreatic cancer patients face a dire outlook, with median survival times under 12 months and only about 2% surviving five years after diagnosis.

48. For patients with advanced or metastatic pancreatic cancer, medical interventions focus on symptom management and extending survival time. As De La Cruz notes, "[t]he primary goals of treatment for advanced pancreatic cancers are palliation and improved survival." Ex. 2014 at 5. Improved survival is considered to be improvement in median overall survival of weeks to months in this patient population. *Id.* ("Because the most recent phase III trials improve survival by only several months . . . the treatment of advanced disease remains controversial."). For patients with metastatic disease, where untreated survival is measured in weeks to months and five-year survival rates are very low, therapeutic interventions that extend life by even a matter of weeks are not merely incremental—they are clinically

significant advances that provide patients with valuable additional time and are considered worthwhile treatment options by the oncology community.

49. Treatment strategies in 2015 for this population of patients encompassed chemotherapy, radiation therapy, and individualized therapeutic approaches. *See* Ex. 2006 at 5. However, the only treatments that had shown benefit in controlled clinical trials and been approved for use by the FDA were chemotherapy treatments. Over the years, the landscape of chemotherapy for metastatic pancreatic cancer has undergone changes as new drugs have emerged for both standalone and combination therapies.

50. Given the poor prognosis of pancreatic cancer, treatment goals may differ depending on the health and ability of the patient to undergo chemotherapy. In frail patients, or patients with considerable comorbidity, supportive care is often the best course of action, even when tumors are potentially curable. Ex. 1050 at 2. When treatment is being given with the goal of long term benefit, “it is important to try to maintain dose intensity, because in both [curative and adjuvant] situations there is a steep dose-response curve, and a small decrease in dose intensity can lead to significant decrease in response and cure rates.” *Id.* In light of this, especially in the context of first-line chemotherapy, where the benefit is potentially greatest, it is important to administer the maximum tolerable dose of the therapeutic agents to the patient. It is for this reason that dose escalation clinical studies are performed to

determine what that maximum tolerable dose is for any particular drug or regimen. For example, such studies were performed for the drugs in the FOLFIRINOX regimen. *See* Ex. 2038 (Ychou).¹

51. For approximately two decades, 5-fluorouracil (“5-FU”) represented the only available chemotherapeutic option for advanced pancreatic cancer. Ex. 2015 at 3. While several clinical studies demonstrated that chemotherapy provided modest survival benefit and improved quality of life compared to best supportive care alone, the impact remained limited. *Id.* Combination approaches pairing 5-FU with other agents failed to show superiority over single-agent treatment. *Id.* (“Several clinical studies could show that chemotherapy in advanced pancreatic cancer patients indeed leads to a modest survival benefit as well as improved quality of life (QoL) compared to best supportive care alone, but the combination of 5-FU with other drugs did not prove to be superior to the single anti-metabolite treatment.”). During this period, median survival for patients with advanced disease remained around 4-5 months, with dismal one-year survival rates. *Id.*

¹ Ychou, authored by the same group as Conroy, explicitly sought to determine the “recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors.” Ex. 2038 at 1. Based on the safety and efficacy results of Ychou’s dose-finding study, the authors recommended “doses of 85 mg/m² for oxaliplatin and 180 mg/m² for irinotecan.” *Id.* at 7-8.

52. In 1997, gemcitabine gained prominence as the preferred first-line treatment for pancreatic ductal adenocarcinoma (“PDAC”) due to its improved tolerability compared to earlier options and demonstrated survival advantages when compared to 5-FU. *Id.* at 3 (“In 1997, gemcitabine became the first line choice for PDAC patients due to fewer side effects (compared to 5-FU) and a significant survival benefit.”). In particular, gemcitabine demonstrated a statistically significant survival advantage over 5-FU (5.65 vs. 4.41 months median OS, $p=0.0025$), and 18% of gemcitabine-treated patients survived to 12 months compared to only 2% with 5-FU, establishing gemcitabine as the new standard of care. *Id.* The drug’s more favorable toxicity profile compared to 5-FU further supported its adoption by the community.

53. Despite gemcitabine’s success, subsequent efforts to improve overall survival outcomes through combination strategies largely did not succeed. Numerous Phase II and III trials evaluated gemcitabine paired with platinum derivatives (cisplatin, oxaliplatin), topoisomerase inhibitors (irinotecan), and other agents. *Id.* at 4; *see also* Ex. 2072 ((Oberstein) at 5 (Table 1)). While some combinations showed promising response rates or progression-free survival benefits in individual studies, most failed to demonstrate statistically significant overall survival improvements with some exceptions, and no alternative combination regimen became widely adopted nor the standard of care during this time. *Id.*

54. Dr. Ratain opines that combination therapy was “commonly used to treat pancreatic cancers.” Ex. 1002 at ¶¶ 63-64. While I generally agree that efforts were made to treat pancreatic cancer through the use of combination therapy as reflected in my discussion above, I disagree to the extent that Dr. Ratain suggests that “combination therapy,” generally, was the standard of care for treating metastatic pancreatic cancer. Nor does Dr. Ratain provide any articulation of what he refers to as “commonly used” or “commonly prescribed,” much less any specific combination therapy in “common” use. Dr. Ratain points to “seven drugs that were commonly prescribed,” yet admits that of those seven only three had received FDA approval for the treatment of pancreatic cancer—5-FU, gemcitabine, and nab-paclitaxel. *Id.* As of August 21, 2015, only gemcitabine and nab-paclitaxel had been routinely used as a combination therapy with gemcitabine, and was considered a “preferred treatment” for metastatic pancreatic cancer (as I discuss below). Dr. Ratain states that gemcitabine in combination with erlotinib while “approved for first-line therapy . . . was rarely prescribed for [metastatic pancreatic cancer], given its minimal benefit.” *Id.* at ¶ 64.

55. Dr. Ratain then opines that “[w]hile 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.” *Id.* (citing Conroy). Conroy, however, does not support his opinion that these drugs were “widely used.” Conroy,

instead, reports a few studies demonstrating that irinotecan had “some clinical activity against advanced pancreatic cancer,” and oxaliplatin has “clinical activity against pancreatic cancer only when combined with fluorouracil.” Ex. 1003 at 2. Such statements do not support Dr. Ratain’s conclusion that these were “widely used,” outside of their use in the FOLFIRINOX regimen. The March 2015 NCCN Guidelines demonstrate that irinotecan (outside of the FOLFIRINOX regime) was not a “preferred” or “other option.” *See* Ex. 2036 (March 2015 NCCN Guidelines)² at 16. Oxaliplatin in combination with fluoropyrimidine, however, was an option listed for clinicians to treat metastatic disease in patients with good performance status. *Id.*

B. FOLFIRINOX and Modified FOLFIRINOX Treatments

56. In 2011, FOLFIRINOX emerged as a leading first-line therapy choice for metastatic pancreatic cancer patients, after clinical trial data demonstrated superior overall survival outcomes (11.1 months compared to 6.8 months) when measured against gemcitabine treatment. *See* Ex. 1003 at 1; Ex. 1041 at 2-3 (describing Phase III PRODIGE 4/ACCORD 11 study data); Ex. 1042 at 1. This chemotherapeutic protocol consists of four distinct agents administered at specific

² The NCCN Guidelines are an important resource for oncologists, and are commonly referenced by POSAs (including myself) for recommendations in the treatment of cancer. As of August 21, 2015, a POSA would have been very familiar with the NCCN Guidelines and used them as a resource in his or her practice.

dosages: oxaliplatin at 85 mg/m², irinotecan at 180 mg/m², leucovorin at 400 mg/m², and 5-fluorouracil given as both a 400 mg/m² bolus injection and a subsequent 2,400 mg/m² continuous infusion over 2 days. *Id.* at 3. This regimen is administered every 2 weeks to patients. *Id.*

57. Despite being associated with a survival advantage over gemcitabine, FOLFIRINOX was known to present toxicity concerns, relative to gemcitabine. *See* Ex. 1003 at 1.

58. Following FOLFIRINOX's establishment as a preferred first-line treatment approach, clinicians began employing modified dosing strategies for its individual components to mitigate the toxicity concerns associated with this combination chemotherapy protocol. *See, e.g.,* Ex. 2004 at 3 ("Oncologists in the United States and elsewhere were anxious to use FFX, but initially concerned about toxicity A Canadian report suggested that there could be considerable toxicity when the regimen is used outside of a clinical study With this scenario in mind, many modifications have been made.").

59. I have prepared a table with exemplary prospective and retrospective studies evaluating modified FOLFIRINOX regimens, including studies that post-date August 21, 2015. *See* Appendix B.

60. In general, a review of the studies that took place prior to the filing date of the '552 Patent demonstrates that the most prevalent modifications to the

FOLFIRINOX regimen were (1) the removal of 5-FU bolus and (2) a dose reduction of irinotecan from 180 mg/m² to a range between 135 and 165 mg/m². *See generally* Appx. B (Vasile, James, Mahaseth, Blazer, Ghorani). Most of the studies maintained the original FOLFIRINOX doses for oxaliplatin at 85 mg/m² and leucovorin at 400 mg/m², and notably none of the studies adjusted the starting oxaliplatin dose to 60 mg/m². *Id.* A POSA would understand, therefore, that a preemptive dose reduction of oxaliplatin was among the less frequently practiced FOLFIRINOX modifications.

61. Overall, the studies of the modified FOLFIRINOX regimens demonstrate that clinicians were willing to make modifications to the original regimen for each of the four components, including oxaliplatin and leucovorin, in order to address toxicity concerns or to treat sensitive patient populations, provided efficacy was maintained. Clinicians did not depart majorly from the traditional FOLFIRINOX regimen. Further, the studies demonstrate that clinicians did not replace any of the ingredients of the FOLFIRINOX regimen with a different active ingredient, much less liposomal irinotecan. This is consistent with my experience. A POSA would not take major dose reductions and/or major modifications lightly, as a POSA would understand that while addressing toxicity, they may negatively impact efficacy.

62. In my experience, most clinicians at the time of the filing of the patents-in-suit administered the original starting doses of the FOLFIRINOX regimen

without modification to patients with metastatic pancreatic cancer and only subsequently reduced doses of various components if required due to observed toxicity events. I disagree that such modifications were “common” as Dr. Ratain opines (Ex. 1002 at ¶ 67) in the sense of them being the standard of care of patients with metastatic pancreatic cancer.

63. In fact, the March 2015 NCCN Guidelines recommend to clinicians that the “preferred” first line treatment for metastatic pancreatic cancer is FOLFIRINOX or gemcitabine/nab-paclitaxel or a clinical trial. Ex. 2036 at 16. The March 2015 NCCN Guidelines further state that while there are “some concerns about the toxicity of the FOLFIRINOX regimen,” “no toxic deaths have been reported” and “[a] more detailed analysis of the quality of life of patients . . . has been published and shows that FOLFIRINOX maintained and even improved quality of life more than gemcitabine did.” *Id.* at 56-57. The “more detailed analysis” referenced is an article in which Conroy is a co-author and wherein the authors concluded that “FOLFIRINOX significantly reduces QoL impairment compared with gemcitabine in patients with metastatic pancreatic cancer” and “[f]urthermore, baseline QoL scores improved estimation of survival probability when added to baseline clinical and demographic variables.” Ex. 2039 (Gourgou-Bourgade) at 1. The March 2015 NCCN Guidelines also recognizes that “toxicity of FOLFIRINOX can be managed with a variety of approaches,” including “first-line FOLFIRINOX at 80% dose

intensity with routine growth factor support in carefully selected patients.” Ex. 2036 at 57.

C. Gemcitabine and Nab-Paclitaxel

64. In and around 2013, another combination chemotherapy regimen arose in addition to FOLFIRINOX: nab-paclitaxel and gemcitabine. *See* Ex. 2032 at 1. A Phase II clinical study was carried out to evaluate the benefit of first-line modified FOLFIRINOX versus gemcitabine/nab-paclitaxel in *de novo* metastatic pancreatic cancer. *See* Ex. 2075 (Knox II). The study reported a median progression free survival of 5.1 months for the gemcitabine/nab-paclitaxel patients and 4.0 months for the modified FOLFIRINOX patients. *Id.* Median overall survival was reported as 9.7 months for the gemcitabine/nab-paclitaxel patients and 8.4 months for the modified FOLFIRINOX patients. *Id.* Despite these results, it was known at the time that “the benefit of chemo for advanced PDAC patients remains poor.” *Id.*

D. Onivyde® and NALIRIFOX

65. On October 22, 2015 the FDA approved Ipsen’s NDA No. 207793 for the use of Onivyde® (irinotecan liposome injection), in combination with 5-fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy (also known as “second-line therapy”). This three-drug regimen is referred to as NALIRI. Onivyde® in combination with fluorouracil, leucovorin, and

oxaliplatin comprises the chemotherapy regimen known as “NALIRIFOX.” *See* Ex. 2032 at 2. Liposomal irinotecan has been referred to in the art as “PEP-02” as well as “MM-398.”

66. The NALIRIFOX regimen has been studied in comparison to these prior chemotherapy regimens. Although the NAPOLI-3 trial demonstrated the superiority of NALIRIFOX to the gem + nab-paclitaxel regimen, there have been indirect comparisons to FOLFIRINOX as well. In a recent study, it was disclosed that NALIRIFOX was associated with better progression-free survival (“PFS”) (8.9 months vs. 6.8 months) and an improvement in life year gain (11.97 months vs. 10.95 months) compared to FOLFIRINOX. Ex. 2029 at 1. That study concluded that “[t]he economic value for use of NALIRIFOX is very high and outside of any conventional boundary of acceptable value threshold for treatment.” *Id.* Another study undertook a similar comparative evaluation and concluded that, compared to FOLFIRINOX and a gemcitabine + nab-paclitaxel regimen, “NALIRIFOX was associated with the highest LYs [(life-years)], QALYs [(quality-adjusted life-years)], and cost.” Ex. 2030 at 1. In another recently published study abstract, the NALIRIFOX regimen in the NAPOLI-3 trial “showed numerically improved OS [(overall survival)] compared to [FOLFIRINOX], including [modified FOLFIRINOX], in the real-world setting.” Ex. 2031.

67. Other recent publications indicate that NALIRIFOX has demonstrated superiority in a first-line setting where a modified FOLFIRINOX regimen has failed and thus represents an improvement in not only degree but also in kind, as it demonstrates statistically significant prolongation of survival in this difficult to treat malignancy. For example, the NAPOLI-3 trial demonstrated that “the NALIRIFOX regimen demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival compared with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma who had not previously received treatment in the metastatic setting.” Ex. 2032 at 6. By contrast, data from two trials (PASS-01 and GENERATE) recently showed that a modified FOLFIRINOX regimen failed to show superiority to the same comparator, (nab-paclitaxel and gemcitabine). *See* Ex. 2033 at 3 (“In PASS-01, the still-maturing data show that GnP is superior to mFFX; similarly, the GENERATE study, which was designed to establish the superiority of mFFX . . . over GnP, closed early for futility.”); Ex. 2034 at 1 (concluding that “GnP is recommended as the first-line treatment for [patients] with [metastatic pancreatic cancer] compared to mFOLFIRINOX”); Ex. 2075 at 1 (reporting that “[m]edian OS [] was 9.7 mo with GnP and 8.4 mo with mFFX”). Overall, “NALIRIFOX led to better outcomes than GnP, but [a modified FOLFIRINOX regimen] failed to do so.” Ex. 2033 at 3.

68. On February 13, 2024, the FDA granted Onivyde® supplemental approval in combination with oxaliplatin, fluorouracil and leucovorin, for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma, based on the results of the NAPOLI-3 clinical trial. *See* Ex. 2040 (FDA Approval Letter).

E. Response to Dr. Ratain’s “A POSA Understood How To Create Different Combination Regimens”

1. Response to “A POSA Regularly Modified FOLFIRINOX Doses”

69. Dr. Ratain opines that “[i]t was frequently necessary to reduce doses of the drugs in the FOLFIRINOX regimen” as result of toxicity issues. Ex. 1002 at ¶¶ 69-72 (relying on Ex. 1003 (Conroy); Ex. 1005 (Mahaseth); Ex. 1041 (Conroy 2013); Ex. 1043 (Blazer)). Specifically, Dr. Ratain points to (1) the removal of the 5-FU bolus (citing to Ex. 1005 (Mahaseth); Ex. 1041 (Conroy 2013)); (2) reduction of irinotecan and oxaliplatin “either at the start of treatment or after observing toxicities” (citing to Ex. 1041 (Conroy 2013) and Ex. 1043 (Blazer)); and/or (3) for elderly and frail patients, removing the 5-FU bolus and reducing both oxaliplatin and irinotecan doses to 50 mg/m² and 135 mg/m², respectively (citing to Ex. 1044 (Alessandretti). Ex. 1002 at ¶¶ 70-72.

70. As I discussed above in Section VI (B) of my declaration, modifications were made to the FOLFIRINOX regimen by clinicians to address toxicity issues. The most prevalent modifications to the FOLFIRINOX regimen as of the ’552 Patent

were (1) the removal of 5-FU bolus and (2) a dose reduction of irinotecan from 180 mg/m² to a range between 135 and 165 mg/m². *See supra* at ¶ 60. Dr. Ratain's references do not contradict my general opinions regarding such modifications.

71. For example, Conroy 2013 (Ex. 1041) states that the “[d]eletion of bolus 5-FU and dose reduction of irinotecan, owing to the presence of the UGT A1*28/28 genotype, were the commonest modifications.” Ex. 1041 at 4. Further, most of the dose studies reported in Conroy 2013 did not have dose adjustments for oxaliplatin at all and when reduced were not reduced to the 60 mg/m² dose claimed in the '552 Patent. Conroy 2013 confirms that, even though clinicians modified the regimen, “FOLFIRINOX is now the reference treatment in patients with good performance status and is cost-effective.” *Id.* at 6. Thus, while a POSA would understand that dose reductions to the various components of FOLFIRINOX took place under certain conditions if so desired, the standard of care at the time of the filing of the '552 Patent was to follow the FOLFIRINOX regimen (not a modified form of it) as I explained above. *See supra* at ¶ 61.

72. Similarly, and as I discuss in more detail below, Mahaseth removed the 5-FU bolus and taught that its modification was well-tolerated. *See infra* at ¶ 165. To the extent a POSA would have been motivated to address toxicity concerns in the FOLFIRINOX regimen, Mahaseth teaches that such toxicity may be addressed by

the specific modifications proposed therein—the removal of the bolus of 5-fluorouracil and adding hematopoietic growth factor. *See infra* at ¶ 167.

73. Blazer’s modifications removed the 5-FU bolus and lowered irinotecan to 165 mg/m² but left oxaliplatin unchanged. Ex. 1043 at 1. While Blazer states that “[t]oxicities lead to dose reductions in 46% of patients,” it does not present any information as to which components were reduced and to what extent. *Id.* It is worth noting that the patients in this study did not have metastatic pancreatic cancer; rather, were patients with borderline-resectable pancreatic cancer and locally advanced unresectable pancreatic cancer. *Id.*

74. Finally, Dr. Ratain points to Alessandrati as teaching doses of oxaliplatin at 50 mg/m² and irinotecan at 135 mg/m². Ex. 1002 at ¶ 72. Alessandrati does not support that conclusion and in fact does not provide any recommendation as to the appropriate modification to FOLFIRINOX. Rather, it states “[m]odified attenuate-dose of FOLFIRINOX needs to be further investigated.” Ex. 1044 at 2.

75. Overall, I agree that a POSA would have been aware of the modifications made to the FOLFIRINOX regimen in various studies. However, a POSA would not have been guided as I explain herein to have further modified the FOLFIRINOX regimen, much less to arrive at the specific invention claimed in the ’552 Patent with a reasonable expectation of success. *See infra* at Section XI.

2. Response to “POSAs Regularly Created Other Combination Regimens Based on The Standard Chemotherapy Drugs”

76. Dr. Ratain opines that, “[a]s apparent from the discussion of the drug regimens above, combinations of these drugs [(i.e., irinotecan, oxaliplatin, leucovorin, and 5-FU)] were widely prescribed for gastrointestinal malignancies, including pancreatic cancer. Ex. 1002 at ¶ 73. I disagree that combinations of these regimens “were widely prescribed” for pancreatic cancer as of the filing of the ’552 Patent with the exception of FOLFIRINOX which was a standard of care treatment. None of the modified FOLFIRINOX regimens that were investigated became standard of care treatments. While clinicians investigated modifications of FOLFIRINOX, those studies do not demonstrate that they were “widely prescribed” or the recommended first-line treatment for patients.

77. Dr. Ratain opines that “modifying drug regimens to develop new treatments” “was a typical practice.” Ex. 1002 at ¶ 74. He states that “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.” *Id.* As an initial matter, none of the references Dr. Ratain points to in support demonstrate that the individual drugs were used in combination or that a POSA would have had “extensive knowledge” as to how those drugs would interact when combined, much less at any specific dose. Rather, the citations are all

to the FDA labeling for each component. It is unclear to me what Dr. Ratain would understand a POSA to know about such drugs or combinations of such drugs based on the labeling alone.

78. Dr. Ratain points to Cantore as an exemplary combination of 60 mg/m² of oxaliplatin and 60 mg/m² of irinotecan. Ex. 1002 at ¶ 76. As I explain below, Cantore would not have guided a POSA to use these doses of oxaliplatin or irinotecan for the treatment of pancreatic cancer in combination with 5-FU and leucovorin as a modified FOLFIRINOX regimen or as guidance to arrive at the claimed invention. *See infra* at ¶¶ 193-200. Indeed, later studies using these two agents used **higher** doses of each—85 mg/m² of oxaliplatin and 150 mg/m² of irinotecan. *Id.* at ¶ 200.

79. While studies were conducted with certain combinations of irinotecan, oxaliplatin, leucovorin, and 5-FU, including the ones pointed to by Dr. Ratain (e.g., IFL, FOLFIRI, FOLFOX, and FOLFOXIRI), as I explain below, a POSA would not have been guided by these combinations to arrive at the specific invention claimed in the '552 Patent with a reasonable expectation of success. *See infra* at Section XI.

3. Response to “When Creating a New Combination, a POSA Understood Dose Reductions to Be Common Practice”

80. Dr. Ratain makes several unsupported broad statements about what a POSA would understand regarding the use of dose reductions when developing a new combination therapy. *See* Ex. 1002 at ¶¶ 77-82.

81. First, Dr. Ratain opines that “[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.” *Id.* at ¶ 77 (citing generally to Ex. 1045 (Paller)). Paller, however, does not draw this broad conclusion. Paller is a guidance document that distinguishes between different types of drug combinations based on whether overlapping toxicities or pharmacodynamic/pharmacokinetic interactions are anticipated. *See* Ex. 1045. Paller seems to instead discuss the need to evaluate whether dose reductions are necessary and to consider “overlapping DLTs [(dose-limiting toxicities)]” and whether they “may limit escalation of doses to levels required for optimal activity or may affect dose intensity due to dose reductions when a regimen is administered chronically.” *Id.* at 4. Paller also states that combinations “without overlapping toxicities, without a plausible basis for a pharmacodynamic interaction leading to a DLT, and without a plausible basis for a pharmacokinetic interaction do not require a formal phase I study.” *Id.* at 6. This teaching directly contradicts Dr. Ratain’s opinion that a POSA would expect dose reductions in all new combinations as a matter of course.

82. While I agree dose reductions are a consideration, I disagree that there is a set expectation. The purpose of the article is about the potential factors a POSA should be considering because as Paller states “[t]he design and conduct of the phase

I combination trial present specific challenges, such as the optimum selection of agents to combine among the range of possible combinations; the selection of the appropriate dose and schedule (including which drug or drugs to dose escalate); drug–drug interactions; overlapping toxicities; and logistic and regulatory challenges.” *Id.* at 2. Paller, therefore, supports the position that such studies are complicated and not simply “routine experimentation.”

83. Second, Dr. Ratain opines that “[w]hile 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.” Ex. 1002 at ¶ 77. I agree with Dr. Ratain that a POSA would have been motivated to administer the maximal tolerated dose of a combination for treatment of pancreatic cancer, and the fact that there are an infinite number of maximal dose combinations for any given combination therapy undermines his opinion that finding such a dose of any combination is “routine.” In general, Dr Ratain is making light of the impact of a dose in clinical trials. As a matter of course, the FDA approves agents and regimens at specific doses and then compares all new regimens to the standard reference regimens, not to “an infinite number of maximal dose combinations.”

84. Third, Dr. Ratain opines that “[a]s 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.” Ex. 1002 at ¶ 77

(citing generally the entirety of Exhibits 1047 (Hess), 1048 (Goel), and 1049 (Rachamalla). A POSA would not have considered Phase I or II clinical trial testing to be “routine experimentation.” A POSA would have understood that; and, at best, a POSA would have hoped that a particular combination would be successful, but there would be no reasonable expectation of success. Dr. Ratain’s references do not state otherwise. In fact, Goel states that “[m]any different cytotoxic agents have been evaluated in combination with gemcitabine, but with the exception of gemcitabine and capecitabine no doublet has demonstrated survival benefit beyond gemcitabine alone.” Ex. 1048 at 1. Thus, a POSA would understand that you would have to run the experiment (e.g., clinical trial) in order to have any sense of whether a particular drug combination would work and that there was a high likelihood that any individual clinical trial would fail to show benefit from a new combination therapy.

85. Dr. Ratain then opines that “a POSA would have understood that doses of oxaliplatin in the range of 60-85 mg/m² were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m² FOLFIRINOX dose” and that a POSA would have found “any oxaliplatin dose within the range of 60-85 mg/m² to be obvious considerations.” Ex. 1002 at ¶ 78. He further opines that it would have been “routine experimentation [for a POSA] to determine a maximally tolerated combination of 5-FU, LV, oxaliplatin,

and liposomal irinotecan.” *Id.* Again, Dr. Ratain does not cite to anything for these conclusions. The essence of his opinion here is that multiple dose-escalating studies in patients through clinical trials would be considered “routine experimentation.” I disagree for the reasons I discussed in the preceding paragraph.

86. Dr. Ratain opines that a POSA would have selected a 60 mg/m² dose of oxaliplatin in light of Conroy Protocol because it purportedly was a dose “that had already been demonstrated to be effective in a similar context”—pointing to Conroy Protocol and to Cantore. Ex. 1002 at ¶ 78. As an initial matter, Conroy concluded that the FOLFIRINOX regimen (e.g., 85 mg/m² oxaliplatin) was effective for the treatment of pancreatic cancer. Indeed, as I stated above, the “preferred” standard of care for metastatic pancreatic cancer is FOLFIRINOX; not any modified version. *See supra* at ¶ 61. While Conroy Protocol disclosed dose reductions in the event of certain toxicities, it did not teach a POSA to use a reduced dose preemptively (i.e., as a starting dose), much less a 60 mg/m² dose of oxaliplatin. I have addressed this reference in full below and incorporate that discussion here as well. *See infra* at ¶¶ 146-161.

87. Similarly, I have explained that Cantore does not support Dr. Ratain’s conclusion and that later-published references used a combination of oxaliplatin and irinotecan and treated patients with **higher** doses than 60 mg/m². *See infra* at ¶ 200.

88. Dr. Ratain opines that “[p]reemptive dose reductions are common when the treatment intent is palliative rather than curative” and that clinicians use their “clinical judgment” in consideration of “factors such as age, treatment intent, comorbidities, and the toxicity of chemotherapeutic agents.” Ex. 1002 at ¶¶ 79-80. While a clinician may use his or her judgment to determine whether a dose-reduction is appropriate for a given patient, that does not translate into the factors a POSA takes into account when developing a new treatment regimen for a patient population as a whole.

89. He also states that dose reductions are “common” when using “platinum-containing regimens.” Ex. 1002 at ¶ 81 (citing Ex. 1052 (Shayne)). As an initial matter, Shayne is not specific to oxaliplatin, nor is it referring to the general population (titled “Dose Intensity ... in Older Cancer Patients Receiving Systemic Chemotherapy”). Moreover, as I have discussed in this declaration, most modified FOLFIRINOX regimens maintained the 85 mg/m² oxaliplatin dose. The most prevalent modifications were the removal of the 5-FU bolus and a reduction in the irinotecan dose. Dr. Ratain’s relied-upon reference demonstrate this. *See, e.g.*, Ex. 1005 (maintaining 85 mg/m² oxaliplatin dose).

F. Response to Dr. Ratain’s “A POSA Would Have Understood That Liposomal Irinotecan May Be Superior To Irinotecan”

90. Dr. Ratain opines that, “[a]t 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.” Ex. 1002 at ¶ 83. In my opinion, a POSA would not have been motivated to substitute liposomal irinotecan in the FOLFIRINOX regimen, much less at the specific dose claimed in the ’552 Patent, and certainly would not have had a reasonable expectation of success in doing so.

91. I first note that Dr. Ratain himself does not state that a POSA would have understood liposomal irinotecan to in fact have been superior to irinotecan; instead he simply states a POSA “may” have had that understanding. That is because as of the filing of the ’552 Patent, CSPC has not cited any reference that compared liposomal irinotecan (alone or in combination with other agents) with free irinotecan (alone or in combination with other agents). As such, as of the filing of the ’552 Patent, a POSA would not have known how liposomal irinotecan would have performed in comparison with free irinotecan in a clinical study for the treatment of metastatic pancreatic cancer.

92. Dr. Ratain only draws a conclusion of purported “superiority” of liposomal irinotecan to free irinotecan in pointing to preclinical studies of liposomal irinotecan. Specifically, Dr. Ratain opines that “preclinical studies of MM-398 suggested it was superior to irinotecan,” relying on in vitro and in vivo mouse studies. Ex. 1002 at ¶ 91 (citing to Exs. 1058 (Kim); 1008 (Ko), 1059 (Hann), and 1006 (Bayever)). Dr. Ratain himself, however, states that “[w]hile preclinical

studies often suggested improved antitumor efficacy and tolerability, there was no clear evidence that such formulations [i.e., liposomal formulations] were superior to unencapsulated drugs.” *Id.* at ¶ 84.³ Paller, one of Dr. Ratain’s own references, states that “[t]he level of preclinical data required to predict a benefit in clinical trials is currently unknown, because preclinical studies do not generally predict success of clinical trials.” Ex. 1045 at 2.

93. The preclinical studies relied upon by Dr. Ratain—Kim and Hann⁴—would not have provided a POSA with motivation to use liposomal irinotecan as part of any specific combination of agents, much less information regarding the dose claimed in the ’552 Patent. Each of those references describes studies using liposomal irinotecan on its own. *See* Exs. 1058, 1059. At best, the preclinical studies provide a POSA with information relating to pharmacokinetics of liposomal irinotecan. A POSA would have understood that additional testing would have been

³ Slingerland describes liposomal drug formulations generally, not specific to liposomal irinotecan. *See* Ex. 1056. To the extent that Slingerland discusses liposomal irinotecan, it provides no information on dosage or use in combination with the other components of FOLFIRINOX. *See* Ex. 1056 at 3 (Table 2). The only other combination therapy mentioned is irinotecan and floxuridine. *Id.* A POSA would not be motivated, based on Slingerland, to substitute liposomal irinotecan in any combination therapy with oxaliplatin, let alone FOLFIRINOX.

⁴ Dr. Ratain also refers to Ko and Bayever in Paragraph 91 of his expert declaration. For the reasons I have provided below with respect to these two references, a POSA would not have been motivated to use liposomal irinotecan as claimed in the ’552 Patent. *See infra* at ¶¶ 169-180, 186-192.

required to evaluate liposomal irinotecan as a monotherapy and even more work would need to be done to evaluate its potential in the claimed combination therapy.

94. Additionally, these preclinical studies of liposomal irinotecan highlight that liposomal irinotecan has distinctly different pharmacokinetic properties compared to conventional irinotecan. For example, Kim notes that “[l]iposomal encapsulation of irinotecan dramatically alters the pharmacokinetic profile of SN-38 in the tumor, as well as tumor response, by maintaining SN-38 levels above the response threshold.” Ex. 1058 at 2.

95. I note that Dr. Ratain does not draw any conclusions of purported “superiority” of liposomal irinotecan over free irinotecan based on any clinical study using liposomal irinotecan. The only clinical study Dr. Ratain points to where liposomal irinotecan was administered to patients in comparison with irinotecan is Roy (Ex. 1055). Roy does not support clinical “superiority” of liposomal irinotecan over free irinotecan. Roy reports the results of a Phase II study of liposomal irinotecan, irinotecan, and docetaxel, each administered as a monotherapy for second-line treatment in patients with metastatic oesophago-gastric cancer.⁵ Ex. 1055 at 1. Roy concludes that “[t]he results from recent phase I studies and this phase II study demonstrate that [liposomal irinotecan] is well tolerated and also has

⁵ See also *infra* at ¶ 324 where I discuss how treatment regimens that are effective in one cancer type to not necessarily transfer to another.

comparable efficacy to docetaxel and irinotecan in patients with prior treatment of advanced gastric and GEJ cancer.” *Id.* at 6. Roy then reports that given the limitations of the study, “a significant conclusion cannot be made from these data at this time.” *Id.* Thus, a POSA would not have understood from this study that liposomal irinotecan would have been clinically “superior” to free irinotecan.

96. Further, Roy states that the “results from ongoing studies of [liposomal irinotecan] as a monotherapy and in combination with other cytotoxic or targeted agents in other tumour types will be crucial to establish this novel agent’s utility in the cancer therapeutics armamentarium.” *Id.* While Roy referenced the use of liposomal irinotecan as a combination therapy, the reference was to the then-ongoing NAPOLI-1 study, wherein liposomal irinotecan was being evaluated in combination with 5-FU and leucovorin—not oxaliplatin. *Id.* (citing to footnote 27). It is also worth noting that Roy would not have directed a POSA to the claimed 60 mg/m² dose of liposomal irinotecan. Roy used doses of liposomal irinotecan of up to 150 mg/m². *Id.* at 1, 4. Roy then concluded that “patients who received [liposomal irinotecan] at 150 mg/m² had a numerically better response rate and PFS/OS compared with the patients who received 120 mg/m², suggesting a higher antitumor activity and this dose is worthy of further evaluation in future studies of [liposomal irinotecan].” *Id.* at 6. A POSA would not have been motivated based on Roy (which

is in a different patient population) to combine liposomal irinotecan in the claimed dose with any oxaliplatin-containing therapy, let alone FOLFIRINOX.

97. Roy also shows that liposomal irinotecan has different pharmacokinetic properties compared to conventional irinotecan. Roy concludes “that following infusion of [liposomal irinotecan], there is a higher AUC, lower clearance and smaller volume of distribution for total and encapsulated irinotecan compared with the published pharmacokinetic data for free irinotecan.” Ex. 1055 at 6.

98. Chang describes a pharmacokinetic clinical study of liposomal irinotecan alone and concludes that the maximum tolerated dose is 120 mg/m² every three weeks. Ex. 1054. This is a higher weekly dose than the claimed 60 mg/m² liposomal irinotecan administered every two weeks. *See* Ex. 1001 at claim 1. Notably, Chang contemplates combination of liposomal irinotecan with 5-FU and LV and/or other agents, but not in combination with oxaliplatin. Ex. 1054 at 6. But Chang is clear that “the optimal dosages of PEP02 for such theoretical combinations remain to be determined.” *Id.* A POSA would not be motivated, based on Chang, to include liposomal irinotecan in FOLFIRINOX, much less in the claimed dose of 60 mg/m². A POSA would not have been motivated based on Chang to combine liposomal irinotecan in the claimed dose with any oxaliplatin-containing therapy, let alone FOLFIRINOX.

99. Additionally, Chang further highlights that that liposomal irinotecan has distinctly different pharmacokinetic properties compared to conventional irinotecan. Chang reports “[t]he PK parameters of CPT-11 PEP02 dosing . . . were characterized by slow clearance,” “small volume of distribution,” and “prolonged terminal half-life,” and these “results suggest that the release of irinotecan from liposomes occurred slowly over time.” *Id.* at 4. Chang also states “[t]he elimination of SN-38 was much slower and presented larger interindividual variability than those of PEP02 and irinotecan.” *Id.*

VII. THE ’552 PATENT

100. The ’552 Patent is titled “Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin.” Ex. 1001 at 1 (field 54). The ’552 Patent issued from U.S. Patent Application No. 15/809,815 (“the ’815 Application”), filed November 10, 2017, and claims priority to U.S. Provisional Patent Application No. 62/208,209, filed August 21, 2015. *Id.* at 1-2 (fields 21, 22, 60).

101. The ’552 Patent describes new methods of treating metastatic adenocarcinoma of the pancreas in humans who have not previously received an antineoplastic agent to treat the condition, consisting of the administration of four different chemotherapeutic agents in specific doses and frequency. *Id.* at 1 (Abstract, field 57), 46:64-48:42. Specifically, it describes a new “method of

treating pancreatic cancer” comprising “the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient.” *Id.* at 2:26-29.

102. Ipsen’s Onivyde® product and its use in the NALIRIFOX regimen are embodiments of the ’552 Patent’s claims. As explained above, the NALIRIFOX regimen comprised liposomal irinotecan (Onivyde®) in combination with fluorouracil, leucovorin, and oxaliplatin. *See* Ex. 2032 at 2. As detailed below, the claims of the ’552 Patent are directed to methods of treating metastatic pancreatic cancer comprising the administration of these four drugs in specific quantities, in a specified order of administration.

A. Overview of Claims

103. The ’552 Patent contains 15 claims, of which 2 are independent claims (i.e., claims 1 and 12) and the remainder dependent claims. *See* Ex. 1001 at 46:64-48:42. I understand that the dependent claims contain all the elements of their respective independent claim in addition to the elements recited in the dependent claims.

104. I understand that Petitioners challenge claims 1-15. Among the challenged claims, claims 1 and 12 are independent claims.

105. Claim 1 recites:

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/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (l)-form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Ex. 1001 at 46:64-47:9.

106. 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/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (l)-form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Ex. 1001 at 48:7-19.

107. The independent claims are generally directed to a new combination therapy for the treatment of metastatic adenocarcinoma of the pancreas by administering to a human patient a specific regimen of four chemotherapeutic agents at specific dosages at specific intervals: liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil.

108. The method of claim 1 is directed to a patient population that “has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas.” *Id.* at claim 1. In other words, the claimed method is for “first-line treatment” of patients. This is in contrast to “second-” or “third-line” treatment which instead would involve patients who have been previously treated with one or more agents to treat metastatic adenocarcinoma of the pancreas.

109. Claim 12 recites the same new combination therapy and is directed to a patient population that “has not previously received gemcitabine.” *Id.* at claim 12.

110. The dependent claims further specify the route, timing, and order of administration of the four agents (claims 2-7, 11, 13, 14, *id.* at 47:10-25, 47:41-48:6, 48:20-37), the type of liposomal irinotecan used (claims 8-10, *id.* at 47:26-40), and the co-administration of a corticosteroid and an anti-emetic along with the four-agent regimen (claim 15, *id.* at 48:38-42).

B. Specification

111. The specification of the '552 Patent provides a background of the state of pancreatic cancer as well as a general overview of the available chemotherapy regimens for the treatment of pancreatic cancer. *See id.* at 1:27-2:13 (“Background”).

112. For example, the '552 Patent states that “[p]ancreatic cancer is chemotherapy-resistant, with an extremely poor diagnosis,” and “[g]iven the poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, new treatment options are still needed.” *Id.* at 1:29-46. It states that “[t]olerability of multi-drug regimens is important in cancer treatment,” and “[t]he longer the duration of manageable treatment should translate into improved outcome due to longer drug exposure.” *Id.* at 1:47-50.

113. The '552 Patent states that, “[d]uring the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (FOLFIRINOX).” *Id.* at 1:50-54. It states that, “[h]owever, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity. Therefore, if equally effective double regimens can be identified, patients

may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit.” *Id.* at 1:54-62. The ’552 Patent also states that, “due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules.” *Id.* at 2:3-6.

114. The ’552 Patent then provides a disclosure of a “novel therap[y] useful in the treatment of pancreatic cancer, including the use of *liposomal irinotecan*⁶ in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer.” *Id.* at 1:21-25 (“Technical Field”) (emphasis added). The ’552 Patent states that “[t]he improved antineoplastic therapies can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens.” *Id.* at 2:23-25.

115. The ’552 Patent states that “[t]he tolerability of combinations of MM-398 liposomal irinotecan and oxaliplatin was improved in mouse models when the oxaliplatin was administered one day after the administration of the MM-398” and reports the toxicities associated with MM-398 and oxaliplatin given as monotherapy

⁶ Liposomal irinotecan is referred to in the art as MM-398 and/or PEP02, and “marketed in the U.S. as the FDA-approved product ONIVYDE® in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine therapy.” Ex. 1001 at 2:8-13.

or combined therapy given concurrently or staggered, with oxaliplatin given one day after MM-398 administration. *Id.* at 9:38-56. The '552 Patent discloses that “[t]hese preclinical findings support the therapeutic use of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC.” *Id.* at 9:57-60. These disclosures demonstrate that the invention described therein, including the novel addition of liposomal irinotecan showed promising activity for the safe and effective treatment of pancreatic cancer.

116. It is clear from the disclosures of the '552 Patent as a whole that the inventors' goal was to develop a novel therapy regimen to treat patients with metastatic pancreatic cancer such that those patients would receive some therapeutic benefit or efficacy in order to improve the patients' condition.

117. For example, the '552 Patent discloses a mouse tumor model study of 5-FU and irinotecan wherein “[t]umor cells (PDX 19015 model) were implanted subcutaneously in mice.” *Id.* at 7:57-58. The '552 Patent states that “[t]he addition of 5-FU to MM-398 or non-liposomal irinotecan significantly improved tumor growth inhibition relative to the respective monotherapies,” and “[t]he addition of oxaliplatin to MM-398+5-FU further improves response by significantly delaying tumor progression as compared to MM-398 monotherapy.” *Id.* at 8:8-12.

118. The '552 Patent discloses a proposed Phase II/III clinical study “to assess the safety, tolerability, and efficacy of MM-398 in combination with other anticancer therapies, compared to nab-paclitaxel+gemcitabine, in patients with metastatic pancreatic adenocarcinoma who have not received prior chemotherapy.”

Id. at 21:30-37. The '552 Patent teaches that during the proposed Phase II/III study:

If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

Id. at 33:4-9. The '552 Patent further states, “[f]or each patient, progression free survival time is determined as the time from randomization . . . to the first documented radiographical Progression of Disease (PD) . . . or death from any cause, whichever comes first.” *Id.* at 40:58-63.

119. The '552 Patent discloses that the doses of the drug components in the claims are directed to the starting, or initial doses of the Onivyde® regimen. In Example 3, the '552 Patent specification describes a Phase II trial design wherein:

The starting dose of ONIVYDE will be 60 mg/m², 5FU 2400 mg/m², LV 400 mg/m² and Oxaliplatin either 85 mg/m² or 60 mg/m². Dose reduction will be 25% reduction in all agents for any grade III-IV Hematotoxicity. For persistent toxicities despite the first dose reduction, and additional 25% dose reduction in all agents will occur. Further toxicity will then lead to discontinuation from trial.

Id. at 30:5-11. In another example, the Detailed Description section similarly discloses the claimed dosages in terms of the starting, or initial doses:

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

TABLE 1B

Examples of Reduced Doses of MM-398 and oxaliplatin			
Dose	MM-398 (mg/m ²) (salt)	Oxaliplatin (mg/m ²)	5-fluorouracil (5FU) (mg/m ²)
Initial	60	60	2400
First Reduction	45	45	1800
Second Reduction	35	35	1350

TABLE 1C

Examples of Reduced Doses of MM-398 and oxaliplatin			
Dose	MM-398 (mg/m ²) (salt)	Oxaliplatin (mg/m ²)	5-fluorouracil (5FU) (mg/m ²)
Initial	60	80	2400
First Reduction	45	60	1800
Second Reduction	35	45	1350

TABLE 1D

Examples of Reduced Doses of MM-398 and oxaliplatin			
Dose	MM-398 (mg/m ²) (salt)	Oxaliplatin (mg/m ²)	5-fluorouracil (5FU) (mg/m ²)
Initial	60	60	2400
First Reduction	45	45	2400
Second Reduction	35	35	1800

TABLE 1E

Examples of Reduced Doses of MM-398 and oxaliplatin			
Dose	MM-398 (mg/m ²) (salt)	Oxaliplatin (mg/m ²)	5-fluorouracil (5FU) (mg/m ²)
Initial	60	80	2400
First Reduction	45	60	2400
Second Reduction	35	45	1800

Id. at 13:38-14:50.

C. Prosecution History

120. The '815 Application, filed November 10, 2017 and claiming priority to provisional application No. 62/208,209 filed August 21, 2015, ultimately issued as the '552 Patent. During prosecution of the '815 Application, Patent Owner provided evidence of secondary considerations of non-obviousness of unexpected results when responding to the examiner's obviousness rejections.

121. In response to a Final Rejection dated February 27, 2020, Patent Owner submitted a response on February 25, 2021 wherein it argued that, “[e]ven if a prima facie case of obviousness were to be established regarding any of the pending claims, which Applicant fervently traverses, one or more objective indicia of nonobvious would support a finding of nonobviousness,” including a “[s]urprising[.]” result that “the claimed lower dose combinations and compositions of 60 mg/m² liposomal irinotecan, 60 mg/m² oxaliplatin, 5-FU, and LV are tolerable and despite the lower combined dose achieved unexpected therapeutic effects over that of the standard first-line FOLFIRINOX regimen as reported in Conroy.” Ex. 1098 at 205-06.

122. In support of these unexpected results, Patent Owner cited a 2020 Wainberg abstract, poster, and presentation⁷ which “report data resulting from the

⁷ Z. Wainberg et al., *First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study*, Ann. Oncol.

clinical protocol described in Example 3 of the instant application.” *Id.* at 207. Patent Owner explained that the results described in these references showed that, of the four cohorts studied in the Phase I/II trial, only one cohort was tolerable—and that cohort comprised 60 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin (the doses claimed in the ’815 Application). *Id.* Patent Owner explained that “[t]he cohort of patients treated with the only tolerable dose of oxaliplatin and liposomal irinotecan tested (60/60) unexpectedly resulted in primary efficacy outcomes higher than that of the currently preferred FOLFIRINOX regimen as reported in Conroy. Specifically, the median overall survival (OS) was 12.6 months, the median progression free survival (PFS) was 9.2 months, and the objective response rate (ORR) was 34.4 % for the 32 patients from both the Cohort B and dose-expansion study.” *Id.* at 207-08. They also explained that “[t]hese primary efficacy outcomes are each higher than those reported in Conroy for FOLFIRINOX (i.e., compared to OS of 11.1 months, PFS of 6.4 months, and ORR of 31.6%).” *Id.* at 208. These results demonstrate that the administration of the lower 60 mg/m² doses of liposomal irinotecan and oxaliplatin, along with 5-FU and LV, unexpectedly showed superior

31 (Suppl. 3):S241 doi.org/10.1016/j.annonc.2020.04.076 (2020) (“Wainberg abstract”), and corresponding poster (“Wainberg poster”) and presentation (“Wainberg presentation”) presented at the European Society for Medical Oncology (“ESMO”) World Congress on Gastrointestinal Cancer, July 1-4, 2020. *See* Ex. 1018 (Wainberg).

primary efficacy outcome measures compared to that of the currently preferred first-line FOLFIRINOX regimen.

123. In a subsequent response dated February 25, 2022, Patent Owner reiterated these unexpected results, explaining “[a]n increase of nearly 3 months in progression free survival (with no overlap at all in the 95% confidence interval) is a significant efficacy improvement to the treatment of patients with pancreatic adenocarcinoma, with an increase in mean overall survival of 1.5 months. Additionally, where 9% of patients receiving FOLFIRINOX in the Conroy regimen experienced grade 3-4 sensory neuropathy—a ‘particular concern with oxaliplatin-containing regimens’—no cases were reported by the patients receiving the claimed regimen.” Ex. 1119 at 153. Patent Owner asserted that “[t]hese improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen.” *Id.*

D. Priority Filing Date

124. I understand Patent Owner’s position is that the ’552 Patent has a priority filing date of August 21, 2015, which is the filing date of its earliest priority application, U.S. Provisional Application No. 62/208,209 (“the ’209 Application”). *See* Paper 9 at 13.

125. I understand that CSPC, in its Petition, argued that, “if the Challenged Claims are construed such that the method of treatment requires clinical efficacy,

then none of the parent applications would adequately describe the claims” because, “[a]s detailed by Dr. Ratain, none of these applications demonstrate that the inventors were in possession of a method of treatment that actually results in any clinical efficacy to patients with metastatic pancreatic cancer.” Paper 1 at 37 (citing Ex. 1002 at ¶¶ 216-26).

126. I understand that the PTAB, in its Institution Decision, disagreed that the ’552 Patent required any particular degree of clinical efficacy, and instead held that “‘treatment’ would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.” See Paper 13 at 12-14 (“To the extent that Patent Owner’s position would require some particular degree of clinical efficacy, however, we do not find that position supported by the evidence. We need not address the exact degree of benefit or efficacy obtained, as the level of clinical efficacy is not a claim limitation.”).

127. As I explain below, I agree with the PTAB’s conclusion. Further, in my opinion, the ’209 Application adequately describes the ’552 Patent’s claimed combination therapy for the treatment of metastatic pancreatic cancer wherein that treatment would have more than a *de minimis* therapeutic benefit or efficacy for the treated patients. Because the PTAB held that the proper construction of “treating” and “treatment” does not require some degree of clinical efficacy, I do not address CSPC’s and Dr. Ratain’s arguments that “if the Challenged Claims are construed

such that the method of treatment requires clinical efficacy, then none of the parent applications would adequately describe the claims” (*see* Paper 1 at 36-39; Ex. 1002 at ¶¶ 216-26), but I reserve the right to supplement my opinions should CSPC or Dr. Ratain change their positions.

128. The '209 Application, the disclosure of which is incorporated by reference in the '552 Patent specification (*see* Ex. 1001 at 1:9-17), describes combination therapies that include liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU for the first-line treatment of metastatic pancreatic cancer. *See, e.g.*, Ex. 1015 at [0006], claims 1, 3. The '209 Application defines the terms “effective amount” and “therapeutically effective amount” as “an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.” *Id.* at [0037]. As the '209 Application describes, these combination therapies are for the treatment of metastatic pancreatic cancer, with clinical effects described by reference to outcome measures. *See, e.g., id.* at [0090]-[0107] (listing several “[r]esponses to therapy” and stating that, “[i]n exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of pancreatic cancer”). These outcome measures amount to providing more than a *de minimis* therapeutic effect on the patient, required by the

“treatment” component of the ’552 Patent claims, as interpreted by the PTAB in its Institution Decision. The ’209 Application moreover describes a regimen that includes each of the claimed drugs in the recited dosages, administered in accordance with the recited frequency. *See, e.g., id.* at [0075]-[0080], [0287]-[0288], claims 4-12. In view of at least these disclosures, a POSA would understand the inventors to have been in possession of the claimed methods at the time of the ’209 Application’s filing.

VIII. PERSON OF ORDINARY SKILL IN THE ART

129. For purposes of this Declaration, I have been asked to apply the following definition of a POSA, proposed by CSPC and Dr. Ratain, with respect to the ’552 Patent as of the priority filing date, August 21, 2015.

130. Dr. Ratain applies the following definition of a POSA for of the claims of 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.

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.

Ex. 1002 at ¶¶ 45-46; Paper 1 at 26.

131. By applying the above description of a POSA, I am not implying agreement with the proposed POSA at all times moving forward. I reserve the right to supplement my opinion should Dr. Ratain and/or CSPC amend their proposed definition.

132. All of my opinions in this Declaration are from the perspective of a POSA, as defined above. At the relevant time, I possessed at least the qualifications of the POSA as defined above.

IX. CLAIM CONSTRUCTION

133. Counsel for Ipsen asked that I provide my opinions regarding the interpretation of two claim terms recited in the '552 Patent claims.

- “treating” and “treat” (all claims).

134. I understand that Petitioners have asserted that the terms “treating” and “treat,” as used in the '552 Patent claims, should be interpreted as “attempting to cause a therapeutic improvement but not requiring actual efficacy.” Paper 1 at 27, Ex. 1002 at ¶ 49. I also understand that Petitioners rely on Dr. Ratain’s testimony that:

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.

Ex. 1002 at ¶ 50.

135. I understand that the PTAB, in its Institution Decision, disagreed with Petitioners and “agree[d] with Patent Owner that the ordinary understanding of a claim reciting a ‘method of treating metastatic adenocarcinoma of the pancreas’ that comprises ‘administering an antineoplastic therapy to the patient’ in order ‘to treat the metastatic adenocarcinoma of the pancreas’ is that the ‘treatment’ would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.” Paper 13 at 13-14.

136. I adopt the PTAB’s claim interpretation ruling for purposes of the opinions set forth herein. I reserve the right to amend or supplement my opinions herein in the event of future claim interpretation decisions by the Board or should Dr. Ratain and/or CSPC amend their proposed definition.

137. I also agree with the PTAB’s and Patent Owner’s understanding of the terms “treating” and “treat,” based on my personal experience as well as my review of the ’552 Patent and its prosecution history. In my opinion, a POSA would

understand the plain and ordinary meaning of “treatment” as having more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.

138. For example, medical dictionaries define “treatment” as: “the management and care of a patient for the purpose of combating disease or disorder” (Ex. 2017 (Dorland’s Dictionary) at 3); “[m]edical or surgical management of a patient” (Ex. 2018 (Stedman’s Dictionary) at 3); or “1. Medical, surgical, dental, or psychiatric management of a patient. 2. Any specific procedure used for the cure or the amelioration of a disease or pathological condition” (Ex. 2019 (Taber’s Dictionary) at 3). These definitions highlight that a POSA would understand that to “treat” a patient in this context requires more than a *de minimis* therapeutic benefit to the patient.

139. I use the terms “treat” and “treating” in a similar way in my own every day practice. When administering “treatment” to metastatic pancreatic cancer patients, the goal is always that such treatment will have more than a *de minimis* therapeutic benefit or efficacy for that patient. While some patients may not receive a therapeutic benefit, the intention behind any treatment is for such benefit to occur.

140. The ’552 Patent itself as well as the prosecution history of the ’552 Patent further support this understanding of the two terms.

141. For example, the claims of the ’552 Patent state that the claimed method involves a “method of ***treating*** metastatic adenocarcinoma of the pancreas . . . the

method comprising ***administering*** [the claimed regimen].” See Ex. 1001 at 46:64-47:9 (claim 1), 48:7-19 (claim 12) (emphasis added). In my opinion, a POSA would understand that “treating” as used in the claims means more than merely “administering” a particular regimen without any hope of therapeutic effect or efficacy, as the claims use both “treating” and “administering” in different places, thus signifying that they carry different meanings. Further, the claims describe the patients in a way that indicates to a POSA that the “treatment” was intended to have more than a *de minimis* therapeutic benefit or efficacy by claiming “a human patient who has not previously received an antineoplastic ***agent to treat the metastatic adenocarcinoma of the pancreas***,” and noting that the therapy provided is an “antineoplastic therapy.” *Id.* at 46:64-47:9 (claim 1) (emphasis added); see also *id.* at 48:7-19 (claim 12) .

142. The specification of the ’552 Patent also supports my opinions. First, for example, the ’552 Patent discusses the background of the invention in terms of the “extremely poor prognosis” that metastatic pancreatic cancer presents to a patient, and a hope that the invention “treatment” might “translate into improved outcome” in patients. Ex. 1001 at 1:29-50. The ’552 Patent specification background also describes the toxicity limitations in the then-existing standard of care for first-line treatment of metastatic pancreatic cancer (the FOLFIRINOX regimen), noting “if equally effective double regimens can be identified, patients

may be able to tolerate prolonged *treatment* better, and even poor performance status patients may receive benefit.” *Id.* at 1:59-61 (emphasis added). These statements teach a POSA that “treating” and “treat” as used in the ’552 Patent would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.

143. The ’552 Patent also discloses a study of 5-FU and irinotecan in a mouse tumor model, wherein the ’552 Patent specification discloses that “[t]he addition of 5-FU to MM-398 or non-liposomal irinotecan significantly improved tumor growth inhibition relative to the respective monotherapies,” and “[t]he addition of oxaliplatin to MM-398+5-FU further improves response by significantly delaying tumor progression as compared to MM-398 monotherapy.” *Id.* at 8:8-12. In my opinion, this disclosure teaches a POSA that the purpose of the administration of the chemotherapeutic agents in the invention is to produce some therapeutic benefit or efficacy to the cancer in the patient being treated.

144. The ’552 Patent also discloses a proposed Phase II/III clinical study to assess the safety, tolerability, and efficacy of MM-398 in combination with other anticancer therapies against nab-paclitaxel+gemcitabine, wherein the ’552 Patent specification discloses that during said study:

If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient’s continuation on study should be discussed between Investigator and

Sponsor or its designee regarding risks and benefits of continuation.

Id. at 33:4-8. The '552 Patent further states, “[f]or each patient, progression free survival time is determined as the time from randomization . . . to the first documented radiographical Progression of Disease (PD) . . . or death from any cause, whichever comes first.” *Id.* at 40:58-63. In my opinion, these disclosures teach a POSA that the purpose of the “study treatment” is to produce some therapeutic benefit or efficacy to the cancer of the patient being treated.

145. My opinion is also supported by the prosecution history, during which the '552 Patent applicant cited evidence of the claimed methods' unexpected results, in the form of clinical effects such as prolonged or progression-free survival, safety, and tolerability. *See supra* at ¶¶ 120-123.

X. THE ALLEGED PRIOR ART REFERENCES RELIED UPON BY DR. RATAIN

A. Conroy (Ex. 1003), Conroy Protocol (Ex. 1004), and Conroy Appendix (Ex. 1017)

146. Conroy is an article describing a Phase II/III clinical trial comparing FOLFIRINOX against gemcitabine in first-line chemotherapy of patients with metastatic pancreatic cancer. Ex. 1003 at 1. Conroy was discussed at length during prosecution of the '552 Patent.⁸

⁸ *See* Ex. 1084 at 192, 194-96, 316, 322-33; Ex. 1088 at 59-65; Ex. 1097 at 190-99, 200-01; Ex. 1119 at 11-18.

147. Conroy Protocol is a document titled “Protocol” and purports to be a “trial protocol [that] has been provided by the authors to give readers additional information about their work” for Conroy. Ex. 1004 at 1.

148. Similarly, Conroy Appendix is a document titled “Supplementary Appendix” and purports to be an “appendix [that] has been provided by the authors to give readers additional information about their work” for Conroy. Ex. 1017 at 1.

149. The FOLFIRINOX regimen of Conroy consisted of a starting dose of biweekly administration of 85 mg/m² oxaliplatin, followed by 400 mg/m² leucovorin, 180 mg/m² non-liposomal irinotecan, and fluorouracil administered as a 400 mg/m² bolus dose followed by a 2,400 mg/m² infusion. Ex. 1003 at 3. The FOLFIRINOX regimen of Conroy consisted of administration of oxaliplatin *before* administration of irinotecan.⁹ Conroy evaluated the safety and efficacy of this regimen as compared to weekly administration of gemcitabine, at a dose of 1000 mg/m². Conroy reported that “[t]he median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months).” Ex. 1003 at 6.

⁹ See Ex. 1003 at 3 (“FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector.”).

150. FOLFIRINOX does not include liposomal irinotecan. Conroy, therefore, does not suggest or provide any information regarding treating metastatic pancreatic cancer using liposomal irinotecan at all, let alone provide any information regarding doses of liposomal irinotecan to use for such treatment alone or in combination with other therapeutic agents.

151. Conroy discloses that “[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.” Ex. 1003 at 4. Dr. Ratain states that “Conroy reported that with the above median relative dose intensities, the median overall survival was 11.1 months in the FOLFIRINOX group.” Ex. 1002 at ¶ 98; *see also id.* at ¶ 97. Dr. Ratain also states that the 78% median dose intensity for oxaliplatin “indicate[s] that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m² based on various toxicity events.” *Id.* at ¶ 105. Dr. Ratain seems to be implying that the efficacy of the FOLFIRINOX regimen is somehow attributable to the lower doses of each component as opposed to the starting doses, and that a POSA would have been directed to use lower doses of the various components, including for oxaliplatin.

152. In my opinion, a POSA would not have understood the results of the FOLFIRINOX trial in the way that Dr. Ratain suggests. Indeed, as Petitioners and Dr. Ratain acknowledge, “[a]fter Conroy’s publication, this FOLFIRINOX regimen

[described in Conroy] for first-line therapy in metastatic pancreatic cancer patients became the **gold standard** in this area of therapy.” Paper 1 at 16 (emphasis added); Ex. 1002 at ¶ 232 (referring to the FOLFIRINOX regimen as “the established gold-standard FOLFIRINOX regimen for first-line treatment of metastatic pancreatic cancer”). The regimen that became the gold standard based on the results from Conroy was the one with a starting dose of 85 mg/m² of oxaliplatin, and, although Conroy discloses a median relative dose intensity of 78% for oxaliplatin, a POSA would not have been directed to instead start with a dose of 60 mg/m² oxaliplatin.

153. Conroy’s “median relative dose intensity” provides limited information to a POSA. For example, it does not inform how many patients received dose reductions, or how many dose reductions occurred over the course of the study. Nor does it inform whether, or how many, dose reductions of oxaliplatin occurred along with other modifications. Importantly, none of the conclusions of Conroy are connected to a reduced dose of oxaliplatin. Rather, the conclusions of the study are based on a treatment regimen where all patients received at least an initial dose of 85 mg/m² oxaliplatin. *See* Ex. 1003 at 3. At most, Conroy’s disclosure of median relative dose intensity indicates that dose reductions occurred. In my opinion, this would not have motivated a POSA to pursue a treatment regimen comprising 60 mg/m² oxaliplatin, let alone the claimed methods.

154. Conroy Protocol and Conroy Appendix provide dose reduction instructions for irinotecan, oxaliplatin, and fluorouracil in the event of patient toxicity events. Ex. 1004 at 15-20; Ex. 1017 at 3-7. In a few potential toxicity event scenarios, Conroy Protocol and Conroy Appendix suggest the dose of oxaliplatin be reduced from the 85 mg/m² starting dose disclosed in Conroy to 60 mg/m² along with concurrent reductions in the irinotecan and fluorouracil. *Id.* In no instance is a dose reduction of oxaliplatin to 60 mg/m² unaccompanied by reductions in irinotecan and/or fluorouracil. *Id.* In certain toxicity events, no reduction in oxaliplatin dose is specified. *Id.*

155. Specifically, for certain toxicity events, Conroy Appendix directs no dose reduction in oxaliplatin:

- 1st occurrence of granulocytes < 1.5 x 10⁹/L. Ex. 1017 at 4 (“**reduction of [the irinotecan] dose** to 150 mg/m²” and “**delete bolus 5FU**”) (emphasis added);
- 1st occurrence of febrile neutropenia, grade 4 neutropenia during more than 7 days, and/or infection with concomitant grade 3/4 neutropenia. Ex. 1017 at 5 (“**reduce the dose of irinotecan** to 150 mg/m² and **delete the 5FU bolus dose**”) (emphasis added);
- 1st occurrence of diarrhea grade 3-4 or diarrhea + fever and/or neutropenia grade 3-4. Ex. 1017 at 6 (“**reduce the irinotecan dose** to 150 mg/m² and **delete the bolus 5FU dose**”) (emphasis added);
- Mucositis or “hand-foot” syndrome. Ex. 1017 at 7 (“In case of grade 3-4 toxicity, a **reduction in dosages** of 25% of both **bolus 5FU** and of **continuous 5FU** will be carried out for the subsequent cycles”) (emphasis added);

- Cardiac toxicity. Ex. 1017 at 7 (“In case of angina pectoris or of myocardial infarction, **5FU has to be stopped**”) (emphasis added);
- Increase of bilirubin. Ex. 1017 at 7 (“If bilirubin is $>1.5 \times \text{ULN}$, **irinotecan is not recommended**. If chemotherapy is medically indicated, it is necessary to provide a **dose adjustment of irinotecan**.”) (emphasis added); *see also* Ex. 1004 at 18 (specifying dose reduction of irinotecan to 75% and 50%).

156. For other toxicity events, the oxaliplatin dose reduction is specified in combination with other modifications:

- 1st occurrence of platelets $< 75 \times 10^9/\text{L}$. Ex. 1017 at 4 (“**reduce the dose [of oxaliplatin]** to 60 mg/m^2 ” and “**reduce both the bolus and the continuous infusion [of fluorouracil]** to 75% of the original doses”) (emphasis added);
- 1st occurrence of grade 3-4 thrombocytopenia. Ex. 1017 at 5 (“**reduce the oxaliplatin dose** to 60 mg/m^2 and the **continuous 5-FU dose** to 75% of the original dose”) (emphasis added);
- 2nd occurrence of diarrhea grade 3-4 or diarrhea + fever and/or neutropenia grade 3-4. Ex. 1017 at 6 (“**reduce also the oxaliplatin dose** to 60 mg/m^2 and **reduce the dose of continuous 5FU** to 75% of the original dose”) (emphasis added);
- Any other toxicity $\geq$ grade 2, except anemia and alopecia, if medically indicated, depending on the adverse event. Ex. 1017 at 7 (“**reduction of irinotecan** to 150 mg/m^2 and/or **oxaliplatin** to 60 mg/m^2 and/or **5FU** of 25%”) (emphasis added).

157. Dose reduction of oxaliplatin alone is recommended only in two toxicity events, both of which are for the second occurrence of those events, wherein the first instance, irinotecan had already been lowered:

- 2nd occurrence of granulocytes $< 1.5 \times 10^9/\text{L}$. Ex. 1017 at 4 (“**reduce the dose [of oxaliplatin]** to 60 mg/m^2 ” after “**reduction of dose [of irinotecan]** to 150 mg/m^2 ” in 1st occurrence of same);

- 2nd occurrence of febrile neutropenia, grade 4 neutropenia during more than 7 days, infection with concomitant grade 3/4 neutropenia. Ex. 1017 at 5 (“**reduce also the dose of oxaliplatin** to 60 mg/m²” after “reduc[ing] the **dose of irinotecan** to 150 mg/m² and delet[ing] the **bolus 5FU** dose” in 1st occurrence of same).

158. Like Conroy Appendix, Conroy Protocol purports to provide further detail on the clinical study described in Conroy and includes the same dosing guidelines as Conroy Appendix. See Ex. 1004 at 16-18. Like Conroy Appendix, Conroy Protocol indicates that all patients in the FOLFIRINOX arm of the study-initiated treatment with a starting 85 mg/m² dose of oxaliplatin. Ex. 1004 at 14. Accordingly, all patients in the FOLFIRINOX arm received an 85 mg/m² dose of oxaliplatin; only patients with specific toxicity events received a lower dose of oxaliplatin.

159. Conroy Protocol describes “FOLFIRINOX” in terms of the initial or starting doses:

Treatment A: Folfirinox

- Oxaliplatin (Eloxatine®) 85 mg/m² D1 in 2h, subsequently
- Irinotecan (Campto®) 180 mg/m² D1 in 90 min.
- Folinic acid 400 mg/m², D1 in 2h (during irinotecan infusion)
- 5-FU bolus 400 mg/m² D1 followed by continuous 5-FU 2.4 g/m² in total over 46 hours, i.e. 1.2 g/m² on D1 and 1.2 g/m² on D2.

Id. at 14. Conroy Protocol specifically notes “[t]reatment will begin with oxaliplatin 85 mg/m² IV infused over 2 hours.”). *Id.* at 15.

160. In my opinion, a POSA would understand Conroy, Conroy Protocol, and Conroy Appendix, as a whole, to teach the efficacy and safety of the study regimen, which comprised a starting dose of 85 mg/m² oxaliplatin—not the 60

mg/m² oxaliplatin dose given in adverse toxicity events accompanied by concurrent reductions to irinotecan and fluorouracil.¹⁰ In my opinion, a POSA would not draw any conclusions about the efficacy of a starting dose of 60 mg/m² oxaliplatin based on Conroy Protocol and Conroy Appendix's dose reduction instructions.

161. For the same reason, Conroy provides a POSA no expectation of successful efficacy for a regimen where *liposomal* irinotecan is used in place of *non-liposomal* irinotecan, and at a much lower starting dose of 60 mg/m² (compared to Conroy's 180 mg/m²). A POSA would understand that the efficacy reported in Conroy was based on the regimen disclosed therein, which included *non-liposomal* irinotecan at a much higher dose of 180 mg/m² and would be taught nothing about the efficacy of *liposomal* irinotecan at a lower dose of 60 mg/m².

B. Mahaseth (Ex. 1005)

162. Mahaseth is an article describing a retrospective analysis of 60 pancreatic cancer patients, 60% of which had metastatic cancer, treated with a

¹⁰ See Ex. 1002 at ¶ 95 (“Conroy discloses the FOLFIRINOX regimen consisting of 85 mg/m² oxaliplatin given as a 2-hour intravenous infusion, 180 mg/m² irinotecan given as a 90-minute intravenous infusion, 400 mg/m² LV given as a 2-hour intravenous infusion, and 5-FU, first administered as a 400 mg/m² bolus and then 2400 mg/m² 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. 1041 (Conroy 2013) at 2-3 (discussing the FOLFIRINOX regimen employed in Conroy, stating “[t]he FOLFIRINOX regimen included oxaliplatin (85 mg/m²).”).

modified FOLFIRINOX regimen which comprised (1) removing the bolus of 5-fluorouracil and (2) administering hematopoietic growth factor. Ex. 1005 at 1.

163. The components of the modified FOLFIRINOX regimen of Mahaseth compared to the components of FOLFIRINOX as described in Conroy can be seen in the below table:

FOLFIRINOX (<i>see</i> Ex. 1003 at 3)	Mahaseth modified FOLFIRINOX (<i>see</i> Ex. 1005 at 2)
• Oxaliplatin: 85 mg/m² • Leucovorin: 400 mg/m² • Irinotecan: 180 mg/m² • 5-FU Bolus: 400 mg/m² • 5-FU IV: 2,400 mg/m²	• Oxaliplatin: 85 mg/m² w/ 5% dextrose • Leucovorin: 400 mg/m² • Irinotecan: 180 mg/m² • 5-FU Bolus: 0 mg/m² (removed) • 5-FU IV: 2,400 mg/m² • Pegfilgrastim: 6 mg

Notably, as shown above, the two modifications made by Mahaseth were to remove the 5-FU bolus and to additionally administer hematopoietic growth factor. Mahaseth does not teach lowering the dose of oxaliplatin, let alone to 60 mg/m². Mahaseth further is silent as to further dose reductions for irinotecan, let alone replacing irinotecan with liposomal irinotecan.

164. Mahaseth taught to administer the modified FOLFIRINOX regimen as follows:

The modified FOLFIRINOX regimen included oxaliplatin 85 mg/m² in water with 5% dextrose intravenously (IV) over 2 hours, leucovorin 400 mg/m² in normal saline IV over 90 minutes concurrently with irinotecan 180 mg/m² in normal saline IV over 90 minutes, and 5-FU 2400

mg/m² in water with 5% dextrose via continuous intravenous infusion over 46 hours. Patients did not receive bolus 5-FU. On day 3 after chemotherapy, pegfilgrastim 6 mg was administered subcutaneously to each patient. Each cycle of therapy consisted of days 1 and 15 treatments.

Ex. 1005 at 2.

165. Mahaseth teaches that the modified FOLFIRINOX regimen was safe and improved overall efficacy. Mahaseth states that the modified FOLFIRINOX regimen “has an improved safety profile with maintained efficacy in metastatic PC,” and that “[t]he lower incidence of neutropenia and absence of febrile neutropenia are due to the discontinuation of bolus 5-FU and the administration of prophylactic pegfilgrastim.” Ex. 1005 at 1, 4. Mahaseth also reported that removal of the 5-FU bolus and administration of growth hormones was observed to be “well tolerated and has significant activity in metastatic [pancreatic cancer].” *Id.* at 5.

166. The authors additionally report that these modifications to FOLFIRINOX “did not appear to negatively impact its efficacy.” *Id.* at 4. Mahaseth reported that “the median PFS among all patients was 9.9 months,” and “the median PFS for patients with nonmetastatic and metastatic disease was 13.7 months . . . and 8.5 months . . . , respectively.” *Id.* Mahaseth reports that “the median OS among all patients was 16.4 months,” and “the median OS for patients with nonmetastatic and metastatic disease was 17.8 months . . . and 9.0 months . . . , respectively.” *Id.* As Dr. Ratain acknowledged, “[t]hat is an improvement of 7.3 months (PFS) and 6.7

months (OS), respectively,” as compared to the results from Conroy. *See* Ex. 1002 at ¶ 113. But this seems to be a mistaken reading of Mahaseth since in that study the metastatic patients had median OS of 9.0 months which in fact is *inferior* to Conroy. The number of 17.8 months refers to patients with nonmetastatic disease.

167. In my opinion, to the extent a POSA would have been motivated to address toxicity concerns in the FOLFIRINOX regimen, Mahaseth teaches that this may be addressed by the specific modifications proposed by Mahaseth—*by removing the bolus of 5-fluorouracil and adding hematopoietic growth factor*.

168. Dr. Ratain states that “a POSA would have known that lowering dosages was a common strategy to remedy or address toxicity concerns.” Ex. 1002 at ¶ 110. Mahaseth, however, does not provide a motivation to change the FOLFIRINOX regimen in any way other than by removing the bolus 5-FU dose and adding a hematopoietic growth factor. Mahaseth does not provide a motivation to lower the doses of any other component of the FOLFIRINOX regimen. Further, Mahaseth reported that this modified regimen “has an improved safety profile with maintained efficacy in metastatic PC” and “appears to have promising activity with respect to resectability and survival.” Ex. 1005 at 1, 5. In my opinion, Mahaseth provides no motivation to make further modifications to the FOLFIRINOX regimen beyond the modifications reported in Mahaseth itself.

C. Bayever (Ex. 1006)

169. Bayever is an international patent application titled “Methods for Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan,” published as WO 2013/188586 and bearing an international publication date of December 19, 2013. Ex. 1006 at 1. Bayever was discussed at length during prosecution of the ’552 Patent.¹¹

170. Bayever discusses the difficulties and challenges associated with the treatment of pancreatic cancer. It notes “[p]ancreatic cancer’s high mortality rate is due to a dearth of effective therapies and a complete absence of reliably durable therapies.” Ex. 1006 at 2. Bayever notes that, “[b]ecause of the location of the pancreas, pancreatic cancer is typically not diagnosed until a tumor has become large enough to produce systemic symptoms,” and “coupled with the absence of good screening tools and a limited understanding of risk factors, results in patients usually having advanced disease, often advanced metastatic disease, at the time of diagnosis.” *Id.* As a result, “[m]etastatic pancreatic cancer has a dismal prognosis and is almost uniformly fatal, with an overall survival rate of less than 4% at 5 years.” *Id.*

¹¹ See Ex. 1084 at 192, 194-96, 316, 322-23; Ex. 1088 at 59-65; Ex. 1097 at 190-99, 200-01; Ex. 1119 at 11-18.

171. Bayever discloses that, particularly in the field of pancreatic cancer treatment (especially for advanced and metastatic cancer), prolongation of survival on the order of weeks is significant. Bayever describes “[s]ingle-agent gemcitabine” as “the current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma” and notes that, in clinical trials, it “has consistently demonstrated a median prolongation of survival of **5 to 6 months** and a 1-year survival rate of about **20%**.” *Id.* at 3 (emphasis added). This demonstrates that even modest prolongation of survival, measured in months, is an advancement of treatment in the field. Bayever further describes another combination therapy approved for first-line use in advanced pancreatic cancer, erlotinib with gemcitabine, that “resulted in a statistically significant benefit in survival, and improvements in median survival (**6.4 months vs. 5.9 months**), and 1-year survival rate (24% vs. 17%) compared to gemcitabine alone.” *Id.* at 3 (emphasis added).

172. Bayever notes that “[c]linical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative” and concludes that, “[t]hus, there is an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer.” *Id.* at 3-4. These disclosures reflect that a POSA understood that the development of new treatments for pancreatic cancer has a low likelihood of success and that clinical trials do not always lead to improvement in outcome.

173. Bayever discusses the metabolism of irinotecan, and how the complexities of its metabolism leads to an unpredictable dose-effect relationship. Bayever states: that “[t]he pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug”; that “[i]rinotecan is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38”; and that SN-38 clearance via glucuronidation displays “major pharmacogenetic variability.” *Id.* at 3. Bayever concludes that “[t]hese drug properties contribute to the marked heterogeneities in efficacy and toxicity observed clinically with irinotecan.” *Id.* These disclosures indicate that a POSA recognized that the clinically observed efficacy and toxicity of a given dose of irinotecan varies among individuals. A POSA would therefore understand that the dose-effect relationship of liposomal irinotecan is unpredictable at least because of this variability in the patient population.

174. Bayever does not disclose any treatment regimen that includes oxaliplatin, much less oxaliplatin at the '552 Patent's claimed dose of 60 mg/m². Bayever therefore also does not mention the sequence of administration of oxaliplatin relative to any other drug. Bayever's methods of treatment comprise only liposomal irinotecan monotherapy or liposomal irinotecan in combination with 5-FU/leucovorin. *See* Ex. 1006 at 26-27, 32-34. Despite its disclosure that “an urgent

need for improvements in, and effective alternatives to, current therapies” in pancreatic cancer, the invention described in Bayever does not include oxaliplatin as a component. *See* Ex. 1006 at 3-4, 31-32.

175. In my opinion, to the extent Bayever purports to address toxicity concerns with pancreatic cancer treatments, it teaches that these issues can be addressed by the use of liposomal irinotecan alone and/or dose modifications thereof, or a combination therapy that consists of liposomal irinotecan, 5-FU, and leucovorin. Bayever does not address any such toxicity concerns through any combination therapy that includes oxaliplatin. Bayever discloses that toxicity concerns related to irinotecan may be addressed by the properties of liposomal irinotecan. It describes “several attributes that may provide an improved therapeutic index” over free irinotecan, and notes these attributes (including increased local bioactivation) are “believed to result in *reduced drug exposure at potential sites of toxicity* and increased exposure at cancer cells within the tumor.” *Id.* at 10 (emphasis added). Bayever further discloses that “individuals who are homozygous for UGT1A1*28 alleles . . . may be at greater risk of toxicity upon receiving standard doses of irinotecan.” *Id.* at 11. Bayever describes dose reductions of liposomal irinotecan for patients with certain UGT1A1*28 genotypes and/or in response to certain toxicities. *Id.* at 32-33, 37-44. 5-FU dose modifications are set out in sections L and M on pages 42-43.

176. Bayever discloses several examples of liposomal irinotecan studies in mice. Bayever's Examples 1 and 2 describe preclinical pancreatic tumor models in mice treated with either liposomal irinotecan or free irinotecan. *Id.* at 19-20. Bayever's Example 3 describes a similar preclinical pancreatic tumor model in a mouse with escalating doses of liposomal irinotecan. *Id.* at 20. Bayever's Example 4 describes another preclinical pancreatic tumor model in a mouse dosed with liposomal irinotecan. *Id.* at 20-21.

177. Bayever also discloses two examples of Phase I/II studies of liposomal irinotecan. Bayever's Example 5 discloses pharmacokinetic results from a Phase I clinical study and a Phase II clinical trial in gastric patients, comparing doses of 60, 120, and 180 mg/m² liposomal irinotecan against doses of 125 and 300 mg/m² free irinotecan. *Id.* at 21, 61-62. Bayever concluded "[t]he MM-398 PK parameters were not significantly changed when combined with 5-FU/LV." *Id.* at 21. Bayever's Example 6 discloses results from a Phase I dose escalation study involving doses of 60, 80, and 120 mg/m² liposomal irinotecan in combination with 5-FU/LV. *Id.* at 22-25.

178. Bayever's final Example 7 discloses a Phase III study design to compare overall survival following treatment with liposomal irinotecan, with or without 5-FU plus leucovorin, versus 5-FU and leucovorin, specifically in second-line patients with metastatic cancer who have progressed on gemcitabine-based

therapy. *Id.* at 25. Bayever's Example 7 trial design describes three treatment arms, none of which comprises the administration of liposomal irinotecan in combination with oxaliplatin. *See id.* at 26-27. The treatment arms of Example 7 include liposomal irinotecan as monotherapy and also in combination with other drugs:

- Arm A: liposomal irinotecan in a dose of 120 mg/m² every three weeks (patients homozygous for UGT1A1*28 receive an initial dose of 80 mg/m² and, if no toxicity, subsequent dose increases in 20 mg/m² increments)
- Arm B: 5-FU/LV weekly
- Arm C: liposomal irinotecan in a dose of 80 mg/m² every two weeks (patients homozygous for UGT1A1*28 receive an initial dose of 60 mg/m² and, if no toxicity, the dose may be increased to 80 mg/m²); 5-FU/LV every two weeks.

Id.

179. Bayever's Example 7 discloses dosing modifications in the event of toxicity events and depending on a patient's UGT1A1*28 genotype. *See Ex. 1006* at 37-44. Patients that are not homozygous for UGT1A1*28 receive an initial liposomal irinotecan dose of 120 mg/m² every three weeks or else 80 mg/m² every two weeks. *Id.* at 26-27. Bayever discloses dose reductions in these patients in the event of certain toxicities including reduction of the liposomal irinotecan dose to 50 mg/m² **and lower** in the event of certain hematological toxicities and diarrhea. *Id.* at 39-41. Bayever's Example 7 discloses that patients homozygous for UGT1A1*28 that receive liposomal irinotecan in combination with 5-FU and leucovorin should

receive an initial dose of 60 mg/m² liposomal irinotecan, but directs the dose of liposomal irinotecan be increased to 80 mg/m² if the patient does not experience any drug related toxicity after the first administration. *Id.* at 26-27. Thus, to the extent that patients homozygous for UGT1A1*28 receive an initial dose of 60 mg/m², the study protocol instructs dose escalation—not dose reduction—in the absence of toxicity.

180. Bayever does not teach or disclose the use of oxaliplatin in any of its examples,¹² much less the use of oxaliplatin in combination with liposomal irinotecan at any particular dose. Bayever also does not mention the sequence of administration of oxaliplatin relative to any other drug. In my opinion, a POSA would not understand Bayever to teach a combination of liposomal irinotecan with oxaliplatin at any dose.

D. Saif (Ex. 1007)

181. Saif is a brief article discussing the results of the Phase III NAPOLI-1 clinical trial which Saif notes compared a combination of liposomal irinotecan,

¹² “Oxaliplatin” only appears in the background section where Bayever notes its use in FOLFIRINOX: “Combination therapies including folinic acid (leucovorin or levoleucovorin), 5-fluorouracil, and irinotecan (FOLFIRI), folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX), or, less commonly, a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) are also used to treat some pancreatic cancers.”). Ex. 1006 at 2.

fluorouracil, and leucovorin against a combination of only fluorouracil and leucovorin in patients with refractory metastatic pancreatic cancer. Ex. 1007 at 1.

182. Saif reports only a few discrete results from the NAPOLI-1 trial, including: the overall survival response of the two arms (6.1 months for the combination including liposomal irinotecan and 4.2 months for the combination without); the *p*-value statistical significance of this overall survival result (0.012); the four most common Grade 3 $\geq$ toxicities by percentage; and a statement that “[a] statistically significant advantage for progression free survival was also observed in the [liposomal irinotecan-containing] arm.” *Id.*

183. Saif is silent regarding any additional details of the NAPOLI-1 trial, including: dosing information of the drugs (including the liposomal irinotecan); patient number and demographic information; patient prior treatment history; or any results beyond overall survival. Therefore, Saif does not disclose any particular dose of liposomal irinotecan that is effective and well-tolerated, alone or in combination with any other drugs, much less oxaliplatin.

184. Saif does not disclose any particular regimen for the treatment of pancreatic cancer; it merely reports that a particular three drug combination (liposomal irinotecan, fluorouracil, and leucovorin) at unknown dosages and timing or method of administration resulted in a higher overall survival in an unknown

number of patients of unknown demographics given only two of those drugs (fluorouracil and leucovorin) in a similarly unknown manner.

185. Saif does not mention the combination of liposomal irinotecan with oxaliplatin at all. Indeed, Saif discusses FOLFIRINOX, a combination of 5-FU, LV, oxaliplatin, and irinotecan, as a first-line treatment option. Ex. 1007 at 1. Saif then questions whether “replacing irinotecan in FOLFIRINOX with [liposomal irinotecan]” is worthwhile, given countervailing toxicity concerns. Ex. 1007 at 1 (“However, bone marrow toxicity has to be borne in mind.”). In my opinion, this disclosure teaches a POSA that the combination of oxaliplatin and irinotecan presents distinct toxicity concerns. To me, Saif does not suggest replacing irinotecan in FOLFIRINOX with liposomal irinotecan, much less at the claimed doses. Indeed, Dr. Ratain seems to agree because as he stated in his declaration, “[n]otably, this study did not compare the combination to the established FOLFIRI regimen, which contains free irinotecan instead of [liposomal irinotecan].” Ex. 1002 at ¶ 90.

E. Ko (Ex. 1008)

186. Ko is an article reporting on a Phase II clinical study evaluating liposomal irinotecan as a monotherapy in second-line pancreatic cancer patients who had progressed following gemcitabine-based therapy. Ex. 1008 at 1.

187. Ko discloses liposomal irinotecan monotherapy at a starting dose of 120 mg/m² (the maximum tolerated dose identified in the first in-human Phase I

monotherapy trial), with dose escalation to 150 mg/m² in patients who did not experience drug-related toxicities worse than grade 1, and dose reductions of liposomal irinotecan at increments of 20 mg/m² for certain toxicities “to a lowest dose level permissible of 80 [mg/m²].” *Id.* at 2. The protocol was subsequently amended to allow for a lower starting dose of 100 mg/m². *Id.* at 3. The primary endpoint of the study was 3-month survival rate, relative to the 3-month survival rate reported in a study of patients receiving the best supportive care after first-line gemcitabine-based therapy. *Id.* at 1.

188. Ko concludes that “PEP02 demonstrates moderate antitumour activity with a manageable side effect profile for metastatic, gemcitabine-refractory pancreatic cancer patients.” *Id.* at 1. Specifically, Ko states that “[m]edian progression-free and overall survival was 2.4 and 5.2 months, respectively.” *Id.* at 4. Ko further states, “[n]otably, the study met its primary end point with 75% of patients surviving at least 3 months, including 25% reaching the 1-year mark.” *Id.*

189. Ko states that the liposomal irinotecan monotherapy displayed an efficacy profile “similar to that seen with FOLFIRI in the GISCAD trial for the same patient population,” which regimen included irinotecan, leucovorin, and fluorouracil. *Id.* at 5. Ko also acknowledged: “although PEP02 was generally well-tolerated in most patients, with manageable and predictable toxicities, the majority of subjects did experience at least one grade 3 or higher adverse event.” *Id.* Of the

grade 3 or higher adverse events, neutropenia was the most frequently reported. *Id.* at 3 (Table 2).

190. Ko then concludes that “[t]he results of this clinical trial are encouraging enough to warrant moving ahead with a larger study in a similar patient population, currently ongoing as an international randomised phase 3 trial called NAPOLI-1.” *Id.* at 5. In my opinion, Ko teaches a POSA that the Phase II results were “encouraging” and states that further Phase III trials are warranted. The conclusion of the Phase II study of liposomal irinotecan as a monotherapy in second-line pancreatic cancer patients would not teach a POSA anything about the performance of liposomal irinotecan in Phase III trials, let alone its performance in any combination therapy. Indeed, Ko itself recognized the “limitations that accompany a single-arm study design” and stated that further studies were warranted *Id.* at 5.

191. Dr. Ratain states that the “suggestions [by Ko] are taken to heart by those in the field as Saif, published a year later, conducted the NAPOLI-1 Phase III trial.” Ex. 1002 at ¶ 146. The NAPOLI-I study, however, was not conducted because of Ko’s report of the Phase II trial results. In fact, Ko itself states that the NAPOLI-I study was “currently ongoing.” Ex. 1008 at 5.

192. Ko states that:

Additional studies may explore this [PEP02’s] potential role in the first-line setting and as part of combination

regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

Id. at 5. Dr. Ratain opines that “[a] POSA would have understood this to be a suggestion to use or study liposomal irinotecan in first-line treatments.” Ex. 1002 at ¶ 146. I agree that Ko suggests “explor[ing]” liposomal irinotecan as a monotherapy, including potentially for first-line therapy. However, Ko’s generic suggestion that liposomal irinotecan be “explore[d]” “as part of combination regimens for APC” in “the first-line setting” does not direct a POSA to any particular combination of drugs, much less any particular dose or regimen. Ko does not teach or suggest replacing the irinotecan component in FOLFIRINOX with liposomal irinotecan. In fact, when referencing FOLFIRINOX, Ko instead directs a POSA to investigate the use of liposomal irinotecan with gemcitabine—not in combination with oxaliplatin, 5-FU, and/or leucovorin.

F. Cantore (Ex. 1009)¹³

193. Cantore is an article describing the results of a Phase II study using combination therapy of oxaliplatin and irinotecan in 30 second-line and third-line

¹³ While Dr. Ratain relies on Cantore as a purportedly invalidating reference for Grounds 1 through 3, he does not provide an overview of this reference in Section VIII of his expert declaration (Ex. 1002). In the event Dr. Ratain expands upon his opinions regarding Cantore beyond what is currently set forth in his expert declaration, I reserve the right to respond in kind.

pancreatic cancer patients whose pancreatic cancer had progressed after gemcitabine-based therapy. Ex. 1009 at 1, 3.

194. The study's treatment regimen comprised cyclical administration of oxaliplatin at 60 mg/m² every week followed by irinotecan at 60 mg/m² every week. *Id.* at 2. Cantore did not measure tumor regression or survival metrics in this study. Instead, "the primary efficacy end point used in the current study was clinical benefit derived from measurement of pain, functional impairment and weight loss." *Id.* at 2. Cantore stated that "[p]ain and functional impairment were the primary measures of clinical benefit" and "[w]eight change was considered a secondary measure." *Id.*

195. Cantore reported that "[a] positive clinical benefit response" was observed in only "6 of the 30 patients (20%)." *Id.* at 3. Cantore also reported that "[t]he 6 patients who experienced a clinical benefit response had a median survival of 21 months, which points to the potential value of clinical benefit as a prognostic indicator." *Id.* at 5. The authors report that this studied combination "is a well-tolerated second- or third-line systemic treatment that shows evidence of being therapeutically beneficial[]" in patients with progressive metastatic pancreatic cancer who have a high-performance status and progressive disease despite having previously been treated with a gemcitabine-containing regimen." *Id.* at 5. Cantore then concludes that "[f]uture studies should try higher doses of irinotecan and oxaliplatin in such patients." *Id.* at 5.

196. Dr. Ratain opines that “a POSA would have understood that other art, like Cantore, showed or suggested that these lower dose regimens, including a 60 mg/m² dose of oxaliplatin along with 60 mg/m² irinotecan, were found to be safe and effective in metastatic pancreatic cancer patients.” Ex. 1002 at ¶ 242. In my opinion, Dr. Ratain mischaracterizes the conclusions a POSA would have drawn based on Cantore.

197. For one, Cantore itself states that the trial “was a preliminary investigation in a small group of patients” and that this along with the “absence of a comparative control group [] limit[s] the clinical significance” of its finding. Ex. 1009 at 5. Cantore further reported positive results in 6 patients using non-standard endpoints of pain and functional impairment rather than “hallmark” measurements from stable disease to prolonged survival. *Id.* A POSA would not have broadly concluded the specific treatment to be “safe and effective in metastatic pancreatic cancer patients.”

198. Rather, at best, a POSA would have understood that this specific regimen (or one using *higher doses of both oxaliplatin and irinotecan*) should be further investigated, perhaps in further Phase II or III studies with control groups and the “hallmark” measurements of prolonged survival. Cantore, however, does not provide any information as to what doses of irinotecan and/or oxaliplatin should be used in such investigations.

199. It is worth noting that Cantore purportedly published in 2004—years before Conroy and the introduction of the FOLFIRINOX regimen as the standard in first-line therapy for metastatic pancreatic cancer. It is silent as to liposomal irinotecan, at any dose, alone or in combination with any other drug. In my opinion, a POSA in August 2015 would not have viewed Cantore as teaching state-of-the-art information on pancreatic cancer.

200. In fact, later studies using a combination of irinotecan and oxaliplatin demonstrated the use of *higher* doses of oxaliplatin and irinotecan. For example, a 2010 Phase II study evaluated “the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a salvage treatment for patients with gemcitabine- and 5-FU-refractory pancreatic cancer,” and administered an “IROX” regimen comprising irinotecan 150 mg/m² and oxaliplatin 85 mg/m². *See* Ex. 2041 (Oh). The Oh authors concluded that “[t]he IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who have been previously treated with gemcitabine- and 5-FU-based chemotherapy.” *Id.* at 1. In another, more recent Phase II study, the IROX regimen was studied in metastatic pancreatic cancer patients who failed when using gemcitabine plus S-1 as first-line therapy, with doses of oxaliplatin 85 mg/m² and irinotecan 160 mg/m², which concluded that “IROX had no significant survival benefit over irinotecan monotherapy in our study. However, IROX reduced the risk of disease progression

by 60%, with acceptable toxicity.” Ex. 2042 (Zhang). These studies which came after Cantore show that a POSA instead used *higher* doses of oxaliplatin and irinotecan.

G. Masi (Ex. 1012)

201. Masi is an article reporting the results of a Phase II study of a combination therapy comprising irinotecan, oxaliplatin, leucovorin, and fluorouracil for the treatment of metastatic colorectal cancer in 32 patients. Ex. 1012 at 1.

202. Masi states that in “a previous phase I-II study we demonstrated that the FOLFOXIRI regimen . . . has promising activity and efficacy in metastatic colorectal cancer.” *Id.* Because that regimen, however, “required a chronomodulated infusion of 5-FU, and because neutropenia occurred in 32% of cycles,” Masi conducted the study reported in this article “in order to develop a simplified FOLFOXIRI regimen.” *Id.*

203. The study treatment regimen “consisted of: irinotecan 165 mg/m² in 250 ml of NaCl 0.9% over 1 h, followed immediately by oxaliplatin 85 mg/m² in 250 ml dextrose 5% and l-LV 200 mg/m² in 250 ml dextrose 5%, infused concomitantly over 2 h via a Y-connector, followed immediately by 5-FU 3200 mg/m² infused as a 48-h continuous infusion.” Ex. 1012 at 3. Masi reported that “[t]reatment was repeated every 2 weeks.” *Id.* Masi concluded that “[w]hile the

safety profile seems to be improved in comparison with our previous FOLFOXIRI regimen, the anti-tumor activity and efficacy seem to be maintained.” *Id.* at 6.

204. In my opinion, a POSA would not have looked to Masi for guidance in any modification to the FOLFIRINOX regimen of Conroy, including modifications of components (e.g., replacement of irinotecan with liposomal irinotecan), doses, or sequence of administration, much less to make such modifications with a reasonable expectation of success, for several reasons.

205. *First*, Masi is entirely focused on the treatment of metastatic colorectal cancer, not pancreatic cancer. Masi does not draw any conclusions as to whether its treatment regimen would be safe and effective for patients suffering from metastatic pancreatic cancer at all, much less whether it would be safe and effective as a first-line or second-line therapy in that set of patients. Rather, Masi states that its “simplified FOLFOXIRI regimen represents the experimental arm in the randomized multicenter study currently being conducted . . . , comparing a standard irinotecan + 5-FU/LV combination (FOLFIRI) with FOLFOXIRI.” *Id.* at 6. Therefore, at best, a POSA would have understood that further investigation for this “simplified” regimen was needed before any conclusions could be drawn for the “simplified regimen” itself and, therefore, would not have been provided with any guidance with respect to a different treatment regimen for a completely different patient population.

206. *Second*, Masi states that they “studied a three-drug combination of irinotecan, oxaliplatin and 5-FU/LV (FOLFOXIRI) using the treatment sequence irinotecan → oxaliplatin → 5-FU, because an *in vitro* study on two human colon cancer cell lines showed that synergy occurs only when irinotecan precedes oxaliplatin/5-FU exposure.” *Id.* at 5. A POSA would have understood that the rationale for this sequence was entirely based on work with colon cells and not pancreatic cell lines. A POSA would not have been guided to adopt this sequence of treatment based on Masi’s work with colon cell lines.

207. *Third*, Masi predates Conroy and the emergence of FOLFIRINOX as the first-line standard of treatment of metastatic pancreatic cancer by over six years. As stated above, Conroy teaches a regimen for the treatment of pancreatic cancer wherein oxaliplatin is administered prior to irinotecan. A POSA would not consider the teachings of Masi over those of Conroy in considering the sequence of administration of components in combination therapy for the treatment of metastatic pancreatic cancer.

208. Dr. Ratain states that “[a] POSA would understand that Masi was suggesting that a second-line treatment should be considered as a first-line therapy option.” Ex. 1002 at ¶ 153; *see also id.* at ¶ 156. He draws this conclusion based on Masi reciting that “5-FU/LV, irinotecan, and oxaliplatin, is associated with promising survival” and 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.” Ex. 1002 at ¶ 153 (citing Ex. 1012 at 2).

209. Dr. Ratain, however, ignores that Masi immediately after the above quotations states “[h]owever, it has yet to be determined whether a combination of these three agents is better than giving them sequentially as two lines, and whether a regimen combining these three agents allows their administration at optimal doses.” Ex. 1012 at 2. Masi is not suggesting that in all cases a second-line treatment should be considered as a first-line treatment. Rather, a POSA would understand that further investigation was warranted to determine whether the use of irinotecan, oxaliplatin, and 5-FU/LV in combination is in fact better (and if so, at what doses) than administering them sequentially in two lines of treatment. In fact, as I mentioned above, Masi concluded that its study was safe and seemed to maintain efficacy but that further investigation was needed to determine how its “simplified” regimen would work in the treatment of metastatic colorectal cancer. As I mentioned above, it is silent as to metastatic pancreatic cancer.

H. Ginocchi (Ex. 1016)

210. Ginocchi is an abstract of a study of a modified FOLFIRINOX regimen used in thirty-nine patients with advanced pancreatic cancer. Ex. 1016 at 1.

211. The regimen reported in Ginocchi included a lower dose of irinotecan (150 mg/m² instead of the 180 mg/m² of FOLFIRINOX) and a higher dose of

fluorouracil (2,800 mg/m² instead of the 2,400 mg/m² of FOLFIRINOX). Ex. 1016 at 1. The modified FOLFOXIRI regimen described in Ginocchi, however, did not change the doses of oxaliplatin and leucovorin used from the original FOLFIRINOX regimen. *Id.* Ginocchi reported that 35.9% of patients had neutropenia. *Id.* Ginocchi also reported that “[f]or [the 17] metastatic patients only, response rate resulted 33% with a PFS and OS of 8.4 and 14.8 months, respectively.” *Id.* Ginocchi concluded that “[t]he mFOLFOXIRI regimen as we used resulted feasible and quite well tolerated and it maintained its good activity in metastatic pancreatic cancer.” *Id.*

212. Ginocchi discloses that FOLFIRINOX is “associated with high incidence of grade 3 and 4 toxicities.” Ex. 1016 at 1. As I mentioned above, Ginocchi concludes that the modified regimen disclosed therein (which employed a lower dose of irinotecan and a higher dose of fluorouracil) “resulted feasible and quite well tolerated and it maintained its good activity in metastatic pancreatic cancer.” *Id.* In my opinion, a POSA would not have been motivated to arrive at the doses of liposomal irinotecan, oxaliplatin, or 5-FU/LV based on Ginocchi. For one, as I mentioned above, Ginocchi’s modifications were “quite well tolerated” and “maintained its good activity in metastatic pancreatic cancer.” Further, the modifications made to FOLFIRINOX were to lower the dose of irinotecan but to ***increase*** the dose of fluorouracil and ***to leave unchanged*** the doses of oxaliplatin

and leucovorin. A POSA would not have then been motivated to lower the doses of these other components given the positive findings of the study. At best, a POSA would have understood that any toxicity concerns in the FOLFIRINOX regimen can be addressed by the modifications made by Ginocchi.

213. Dr. Ratain stated that the “claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients,” citing to Ginocchi in support. Ex. 1002 at ¶ 309. It is unclear to me what “sequence of drugs” he is referring to—whether he is referring to claim 1 or another claim of the ’552 Patent. It is my understanding that claim 1 of the ’552 Patent does not recite a specific order or sequence of administration for the claimed treatment regimen. Notably, the components of FOLFOXIRI as well as the doses of that regimen are different from the claimed invention. Therefore, I disagree that FOLFOXIRI has the “same sequence of drugs” as those claimed. Moreover, for claim 2 of the ’552 Patent, Ginocchi does not disclose that “administration of oxaliplatin begins 2 hours after completing each administration of” irinotecan, much less liposomal irinotecan. Ginocchi also does not disclose the administration of a corticosteroid and an anti-emetic prior to the antineoplastic therapy, as required by claim 15.

I. Carnevale (Ex. 1013)

214. Carnevale is a journal article summarizing clinical studies involving liposomal irinotecan for the treatment of pancreatic cancer published in December 2015. Ex. 1013 at 1. I understand from counsel that this publication date is after the August 21, 2015 priority date of the '552 Patent and that the PTAB held that Carnevale is not prior art in its Institution Decision. *See* Paper 13 at 45.

215. Carnevale restates the results of the Phase II clinical study of liposomal irinotecan monotherapy described by Ko (Ex. 1013 at 7) and the results of the Phase III clinical study of a three-drug (non-oxaliplatin-containing) therapy described in Saif (*id.* at 8). In my opinion, Carnevale teaches a POSA nothing beyond the disclosures of Saif and Ko regarding treatment of pancreatic cancer.

216. Carnevale discloses the low likelihood of success in developing new treatments for pancreatic cancer. For example, Carnevale states that “progress in the therapeutic development of this disease has historically taken a slow and painstaking course, littered with numerous negative trial results.” *Id.* at 1. Carnevale further characterizes pre-2010 efforts as a “stretch of failed or clinically inconsequential trials.” *Id.* at 2. In my opinion, Carnevale’s characterization is consistent with a POSA’s particularly low expectations of success in this field.

J. Dean (Ex. 1014)

217. Dean is an abstract of a prospective Phase II comparative study comparing regimens of liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin against the three-drug combination therapy described in Saif and a control arm of nab-paclitaxel and gemcitabine. Ex. 1014 at 3. Dean was published in February 2016. I understand from counsel that this publication date is after the August 21, 2015 priority date of the '552 Patent and that the PTAB held that Dean is not prior art in its Institution Decision. *See* Paper 13 at 45.

218. Dean does not mention dosage amounts for any of the components of any of its proposed regimens. Dean also does not report any results from its prospective studies, and thus does not teach a POSA anything about the efficacy of its proposed regimens.

K. Nichetti (Ex. 1010)

219. Nichetti is a journal article reporting on a retrospective review of Phase III clinical trials involving NALIRIFOX, FOLFIRINOX, and gemcitabine with nab-paclitaxel (“GEM-NABP”). Ex. 1010 at 1. Nichetti was published in January 2024. I understand that Nichetti is not prior art to the '552 Patent, but was cited by Petitioners and Dr. Ratain to support arguments regarding secondary considerations of non-obviousness, including unexpected results. *See* Paper 1 at 34-35, 51-52; Ex. 1002 at ¶¶ 165-68, 260.

220. Dr. Ratain alleges that “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.’” Ex. 1002 at ¶ 167 (citing Ex. 1010 at 1, 5). Dr. Ratain points to statements in Nichetti that

[T]here 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 ¶ 167 (citing Ex. 1010 at 9).

221. In my opinion, Nichetti does not establish that NALIRIFOX and FOLFIRINOX are “identical” in efficacy, or in any other respect, nor does it refute evidence that the ’552 Patent’s claimed methods offer unexpected benefits. Nichetti reflects a review and meta-analysis, “with all the inevitable limitations” inherent to such a study, of data from a number of different clinical trials involving different regimens for treatment of pancreatic cancer. *See id.* at 9; *see also id.* at 10 (section titled “Limitations”). Nichetti also indicates that NALIRIFOX had a superior toxicity profile compared to FOLFIRINOX. *See id.* at 9 (“In terms of safety,

NALIRIFOX was associated with the most favorable toxicity profile, with a lower incidence of hematological toxic effects and peripheral neuropathy, which often represent the limiting adverse events for the other 2 regimens.”). Further, in my opinion, a POSA would not consider a “100-fold” increase in the mean cost per cycle of one component of a regimen to weigh against its benefit in the field of pancreatic chemotherapy. At most, Nichetti teaches a POSA that its findings “may empower a more careful evaluation of these regimens.” *Id.* at 10.

L. Nevala-Plagemann (Ex. 1011)

222. Nevala-Plagemann is a journal article that purports to compare the results of the NAPOLI-3 clinical trial, which was a Phase III clinical trial comparing NALIRIFOX against gemcitabine-nab-paclitaxel in first-line pancreatic cancer, against “historical data,” to opine on whether “the addition of NALIRIFOX to the therapeutic armamentarium for this disease constitutes true progress.” Ex. 1011 at 1. Nevala-Plagemann was published in August 2024. I understand that Nevala-Plagemann is not prior art to the ’552 Patent, but was cited by Petitioners and Dr. Ratain to support arguments regarding secondary considerations of non-obviousness, including unexpected results. *See* Paper 1 at 34-35, 51-52; Ex. 1002 ¶¶ 165-68, 260.

223. Dr. Ratain cites Nevala-Plagemann’s statements 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. 1002 at ¶ 170 (citing Ex. 1011 at 1-2).

224. In my opinion, Nevala-Plagemann does not establish that NALIRIFOX and FOLFIRINOX are “identical” in efficacy, or in any other respect, nor does it refute evidence that the ’552 Patent’s claimed methods offer unexpected benefits. Nevala-Plagemann is an opinion piece (“[w]e argue that” (Ex. 1011 at 1)) which, at most, purports to identify issues for future consideration and study. *See* Ex. 1011 at 2 (“Well-conducted studies analysing real-world data on the clinical uptake of NALIRIFOX could provide evidence that helps to settle this issue. While we look forward to the results of these future studies, whether NALIRIFOX represents true hope for our patients or just hype remains to be seen.”). Nevala-Plagemann admits that its conclusions are based on a 2024 understanding of the state of the art, and thus does not reflect what a POSA would have understood as of the effective filing date of August 21, 2015. *See id.* at 1 (“Considering only the advances in supportive care since the publication of PRODIGE 4 over a decade ago, we would have expected improved outcomes in NAPOLI 3.”).

225. Nevala-Plagemann recognizes that “[d]ata from previous studies suggest that nanoliposomal irinotecan has improved pharmacokinetic properties, including lower clearance, extended half-life and increased accumulation at tumour sites with potential for lower toxicity.” *Id.* at 1. Nevala-Plagemann also recognizes that “PRODIGE 4 limited enrolment to patients of ≤ 75 years of age” and, compared to the “more-relaxed inclusion criteria of NAPOLI-3,” may have affected the similarity in median OS between the two studies. *Id.* Further, Nevala-Plagemann recognized “the higher ORR observed with NALIRIFOX in NAPOLI 3 compared to FOLFIRINOX in PRODIGE 4 (41.8% versus 31.6%)” and the lower incidences of both grade ≥ 3 neutropenia and febrile neutropenia with NALIROFOX compared to FOLFIRINOX (24% versus 46 % and 2% versus 5%, respectively). *Id.* at 1-2.

XI. DETAILED OPINIONS

226. I have been asked to consider whether certain references, discussed below, disclose or suggest limitations recited in certain claims of the '552 Patent. My detailed opinions are set forth below.

A. Ground 1: Claims 1, 3-6, and 8-14 Would Not 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

227. Counsel for Patent Owner asked that I provide my opinions regarding whether CSPC has demonstrated that claims 1, 3-6, 8-14 of the '552 Patent would have been obvious over the references asserted in the Petition and supporting

declaration. In my opinion, for the reasons discussed below, CSPC fails to show that Conroy, Conroy Protocol, Conroy Appendix, and Mahaseth in combination with Bayever, Saif, Ko, and Cantore render obvious claims 1, 3-6, or 8-14.

228. Dr. Ratain opines that claim 1 would have been obvious in light of the FOLFIRINOX regimen “because the claimed method of treatment involves administering an antineoplastic therapy consisting of liposomal irinotecan, oxaliplatin, and 5-fluorouracil – the same four-drug combination” found in FOLFIRINOX. Ex. 1002 at ¶ 232; *see also id.* at ¶ 233.

229. Claim 1 of the '552 Patent and the FOLFIRINOX regimen, however, do not contain the same four drugs and do not contain those drugs at the same dosages. Dr. Ratain clarified during his deposition that by the term “drugs” he meant active ingredients but different drug products. Ex. 2073 (Ratain Deposition) at 48:4-49:6. He agreed that liposomal irinotecan is a different drug product from irinotecan, and required its own FDA approval to be used for the treatment of metastatic pancreatic cancer (alone and in combination with other agents). *Id.* at 49:7-12.

230. In order to arrive at the invention set forth in claim 1, a POSA would have had to make four distinct modifications to the FOLFIRINOX regimen. A POSA would have had to:

1. decrease the dose of oxaliplatin from 85 mg/m² to 60 mg/m²;
2. remove the 400 mg/m² 5-fluorouracil (5-FU) bolus;

3. substitute liposomal irinotecan for irinotecan; and
4. use a 60 mg/m² dose of liposomal irinotecan.

Dr. Ratain opines that a POSA would have been motivated to make these modifications for two reasons: to reduce toxicity of FOLFIRINOX and because of the purported “superior” properties of liposomal irinotecan over irinotecan. *See, e.g.,* Ex. 1002 at ¶ 234 (“reduce toxicity”); ¶ 236 (“superiority of liposomal irinotecan to irinotecan”); ¶ 240 (“aim to reduce toxicity”); ¶ 241 (“reduce toxicity concerns”); ¶ 244 (“improve the toxicity profile”).

231. As an initial matter, I disagree with Dr. Ratain’s opinion because if a POSA were to have made those four modifications for the two reasons he states (which I do not agree a POSA would have made), then, in my opinion, a POSA would at least not have made all four modifications at the same time.

232. Rather, a POSA would have made one modification to the FOLFIRINOX regimen at a time, then tested that change to assess its impact on both toxicity as well as any purported superior efficacy. And, only then, would a POSA have determined whether any further modifications were warranted. This iterative approach is fundamental to rational drug development, particularly when modifying an established regimen with known clinical activity. Making all four changes at once would have made it impossible to determine which modification(s) contributed to any observed changes in the regimen’s safety or efficacy profile.

233. A POSA had no reason to believe that all four modifications were necessary to achieve Dr. Ratain's stated goals of reducing toxicity or creating a regimen with "superior" properties compared to FOLFIRINOX. Indeed, any one of these modifications—such as reducing the oxaliplatin dose or removing the 5-FU bolus—might alone have been sufficient to reduce toxicity. Similarly, substituting liposomal irinotecan might alone have produced superior properties and reduced toxicity without requiring simultaneous dose reductions in other agents. A POSA would not have undertaken the complex task of making four simultaneous changes without first exploring whether simpler, less dramatic modifications could achieve the desired outcomes. For this reason, I believe Dr. Ratain's obviousness conclusion is flawed.

234. For the additional reasons discussed below, I disagree that a POSA would have been motivated to make all four of these changes (much less simultaneously) based on the prior art Dr. Ratain relied-upon as well as in light of the prior art as a whole. I also disagree that a POSA would have had a reasonable expectation of success in doing so.

**(a) Toxicity Concerns Would Not Have Motivated a
POSA to Pursue CSPC's Allegedly Obvious
FOLFIRINOX Modifications**

235. Dr. Ratain opines that a POSA would have been motivated by “toxicity concerns” to (1) lower the 85 mg/m² dose of oxaliplatin and (2) remove the 5-FU bolus dose of the original FOLFIRINOX regimen. Ex. 1002 at ¶¶ 241-44.

236. While I agree that, as of August 2015, Conroy and other references relied upon by Dr. Ratain report toxicity issues with FOLFIRINOX, these references would not have motivated a POSA to modify the regimen in the multiple, specific ways suggested by Dr. Ratain. *First*, neither the Conroy references nor any other prior art Dr. Ratain relies upon teaches or suggests that a POSA should preemptively reduce the starting dose of oxaliplatin from 85 mg/m² to 60 mg/m², as claimed in the '552 Patent. *Second*, a POSA seeking to address FOLFIRINOX's toxicity profile would have been aware of numerous approaches for doing so, each involving far more limited modifications than the four simultaneous changes Dr. Ratain suggests. And, *third*, even if a POSA had been motivated to make multiple modifications to FOLFIRINOX, that POSA would not have had a reasonable expectation of success in combining an untested liposomal irinotecan combination with modified doses of oxaliplatin and 5-FU for the treatment of metastatic pancreatic cancer.

**(i) The Conroy References Do Not Teach
Preemptive Oxaliplatin Dose Reduction, Let
Alone to 60 mg/m²**

237. Dr. Ratain specifically points to Conroy and Conroy Protocol as teaching “the potential need for reduction of oxaliplatin dose” and disclosing “a dose reduction of oxaliplatin to 60 mg/m² oxaliplatin for toxicity.” Ex. 1002 at ¶¶ 241-43.

238. Conroy describes a Phase III study that showed FOLFIRINOX resulted in improved efficacy over the then-standard for treatment, gemcitabine for patients with metastatic pancreatic cancer. As Conroy describes, the FOLFIRINOX regimen that is the subject of this study comprised oxaliplatin, 85 mg/m², irinotecan, 180 mg/m², LV, 400 mg/m², and 5-FU, 400 mg/m² (bolus) and 2,400 mg/m² (infusion). Ex. 1003 at 1. All patients in the study described in Conroy received oxaliplatin at least as a starting dose of 85 mg/m².

239. The study data demonstrated that FOLFIRINOX conferred a survival advantages over gemcitabine. *Id.* Conroy and its results ultimately led to FOLFIRINOX replacing gemcitabine as the standard of care for metastatic pancreatic cancer. *See* Ex. 1041 at 3-4. Thus, Conroy’s conclusion of a significant difference in clinical outcome is for FOLFIRINOX, a treatment regimen comprising 85 mg/m² oxaliplatin. A POSA would associate the results and clinical findings

reported in Conroy as associated with a regimen that includes oxaliplatin in a starting dose of 85 mg/m².

240. A POSA would understand FOLFIRINOX, as described in Conroy itself and as described in subsequent references, to mean a regimen that includes a starting dose of 85 mg/m² oxaliplatin. Conroy 2013, by the same lead author as Conroy, describes experience with FOLFIRINOX after the study described in Conroy. *See* Ex. 1041. Conroy 2013 defines FOLFIRINOX as including 85 mg/m² oxaliplatin. *See, e.g.,* Ex. 1041 at 2 (“The FOLFIRINOX regimen included oxaliplatin (85 mg/m²) over 2 h, . . .”). Other references similarly define FOLFIRINOX as including 85 mg/m² oxaliplatin. *See, e.g.,* Ex. 2004 at 1 (“Promising phase II results with FOLFIRINOX (FFX) (*oxaliplatin 85 mg/m²*, leucovorin 400 mg/m², irinotecan 180 mg/m², bolus 5-fluorouracil 5FU) (400 mg/m², infusional 5FU 2400 mg/m² over 46 h, every 14 days) were confirmed in a sentinel Phase III study (PRODIGE 4/ACCORD 11).” (emphasis added)); Ex. 2007 at 2 (“FOLFIRINOX, a regimen composed of four drugs (Folinic acid 400 mg/m², 5-FU bolus 400 mg/m² followed by 48 h infusional 5-FU 2,400 mg/m², Irinotecan 180 mg/m², and *oxaliplatin 85 mg/m²*)” (emphasis added)).

241. Dr. Ratain also places undue reliance on the reported “median relative dose intensity of 78% for the oxaliplatin administered in the study. *See* Ex. 1002 at ¶¶ 97-98, 105, 241. As I explain herein, Conroy’s “median relative dose intensity”

does not inform how many patients received dose reductions, or how many dose reductions occurred over the course of the study. Nor does it inform whether, or how many dose reductions of oxaliplatin occurred along with other modifications. Nor does it connect the conclusions of the study to a reduced dose of oxaliplatin. Rather, the conclusions of the study are based on a treatment regimen where all patients received at least an initial dose of oxaliplatin, 85 mg/m². *See infra* ¶ 152.

242. At most, Conroy's disclosure of median relative dose intensity indicates that dose reductions occurred during the course of treatment for some patients. This would not have motivated a POSA to pursue a first-line treatment regimen comprising 60 mg/m² oxaliplatin as a starting dose, let alone the claimed methods.

243. Dr. Ratain overlooks that there was a known rationale for the 85 mg/m² dose of oxaliplatin. Conroy cites Ychou et al., a reference that has several co-authors in common with Conroy, in discussing the study rationale. *See* Ex. 1003 at 2.

244. Ychou describes the results of a study aimed at determining the "recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors." Ex. 2038 at 1. Based on the study results, which account for both safety and efficacy, the Ychou authors recommend "doses of 85 mg/m² for oxaliplatin and 180 mg/m² for irinotecan." *Id.* at 7-8. In my opinion, the authors of Conroy appreciated, as would a POSA, the rationale behind the doses employed in FOLFIRINOX.

245. Dr. Ratain also overlooks the significance of a starting, or “defined” dose in the context of treatment. As explained *supra* (see *supra* at ¶ 50), when treatment is being given with the goal of long term benefit, it is important to try to maintain dose intensity, because in both curative and adjuvant situations there is a steep dose-response curve, and a small decrease in dose intensity can lead to significant decrease in response and cure rates. In light of this, especially in the context of first-line chemotherapy, it is important to administer the maximum tolerable dose of the therapeutic agents to the patient. A POSA would understand that a starting, or “defined,” dose is the dose that has been associated with the best clinical outcomes and would not depart from that preemptively, if possible.

246. To the extent that Conroy refers to a lower dose of oxaliplatin, it is in the limited context of dose modification for some patients, in some instances of “predefined toxic events.” See, e.g., Ex. 1003 at 3. Conroy Protocol and Conroy Appendix detail the conditions under which dose reduction might be appropriate. See Ex. 1004 at 15-20; Ex. 1017 at 3-9; see *supra* at ¶¶ 154-157.

247. At most, the Conroy references teach that toxicity events may prompt a dose reduction after treatment has been given, including oxaliplatin, 85 mg/m², and only for some patients, under certain circumstances. This is fundamentally different from preemptively starting all patients at a reduced dose of 60 mg/m².

248. Significantly, and as reflected in Conroy Protocol and Conroy Appendix, not all toxicity events prompted a reduction in oxaliplatin dose. The majority of events call for modifications other than a reduction in oxaliplatin dose. *See supra* at ¶¶ 154-157. Other events called for oxaliplatin dose reduction in combination with other modifications. *See id.*

249. In my experience treating patients with pancreatic cancer, and based on my review of the Conroy references, oxaliplatin dose reduction is not among the recommended modifications for the first occurrence of neutropenia, which was the most commonly reported grade 3 or 4 adverse event. *See* Ex. 1004 at 16-19, Ex. 1003 at 8, Table 3. Dose reduction of irinotecan or 5-FU is generally recommended more frequently than oxaliplatin dose reduction. *See* Appx. B.

250. Conroy, Conroy Protocol, and Conroy Appendix do not teach a starting dose of oxaliplatin, 60 mg/m², nor even that oxaliplatin dose reduction is warranted in all instances of toxicity. In my opinion, a POSA would not have understood the Conroy references to motivate preemptive oxaliplatin dose reduction to 60 mg/m².

251. In summary, Dr. Ratain incorrectly conflates Conroy's dose-modification schedule with the treatment regimen itself. Conroy's treatment regimen is FOLFIRINOX, which includes an 85 mg/m² dose of oxaliplatin as the starting dose. Toxicity events that may arise after administration of at least one 85

mg/m² dose are addressed by the dose-modification schedule, which does not even recommend oxaliplatin dose reduction in the majority of instances.

252. In my opinion, a POSA would not understand the Conroy references to teach the '552 Patent's claimed dose of oxaliplatin or otherwise motivate preemptive oxaliplatin dose reduction to 60 mg/m² as a starting dose for all patients.

(ii) A POSA Would Not Have Been Motivated to Make the Multiple, Specific Modifications to FOLFIRINOX That Would Result in the '552 Patent's Claimed Methods

253. Apart from the Conroy references, Dr. Ratain identifies no other basis for alleged motivation to modify FOLFIRINOX by preemptively reducing the dose of oxaliplatin to 60 mg/m². Bayever, CSPC's other lead reference, is entirely silent on a combination therapy including oxaliplatin, much less in any dosage. *See supra* at ¶ 174.

254. If anything, the prior art as a whole suggests that, among various approaches for addressing toxicity issues, preemptive oxaliplatin dose reduction was not preferred. *See* Appx. B; *see also infra* at ¶¶ 262-269. To the extent that a minority of references suggest preemptive oxaliplatin dose reduction, they do not motivate a POSA to the claimed 60 mg/m².

255. Dr. Ratain's relied-upon references describe approaches for reducing toxicity of FOLFIRINOX by means other than oxaliplatin dose reduction. For example, each of Mahaseth, Ginocchi, and Hatachi cites Conroy and the toxicity

issues observed with FOLFIRINOX. *See* Ex. 1005 at 1; Ex. 1016 at 1; Ex. 1021 at 1, n.4. Each of those references, however, suggests a different approach for reducing toxicity, none of which include preemptive oxaliplatin dose reduction. Mahaseth describes modification by removing the 5-FU bolus and adding a growth factor. Ex. 1005 at 1. Ginocchi describes modification by 5-FU bolus removal and irinotecan dose reduction. Ex. 1016 at 1. Hatachi suggests 5-FU bolus removal only. Ex. 1021 at 1.

256. Dr. Ratain's own references therefore refute the suggestion that Conroy, Conroy Protocol, and Conroy Appendix would have motivated a POSA to modify FOLFIRINOX by preemptively reducing the dose of oxaliplatin, much less to 60 mg/m². In light of these disclosures, a POSA would be motivated to modify FOLFIRINOX—if at all—in a number of ways other than oxaliplatin dose reduction.

257. To the extent certain of Dr. Ratain's references describe preemptive oxaliplatin dose reduction, it is described as a relatively uncommon modification. Conroy 2013 reports on the results of a “multi-institutional experience of FOLFIRINOX,” using a “retrospective and prospective registry.” Ex. 1041 at 4. These results reflect that dose modification to the initial treatment cycle occurred in 50.8% of patients, but that oxaliplatin dose reduction was not the most common. *Id.* Rather, “[d]eletion of bolus 5-FU and dose reduction of irinotecan” were the most common. *Id.*

258. Gunturu also reports the results of a retrospective study and, consistent with Conroy 2013, reports that other modifications in the first cycle of treatment (namely 5-FU bolus removal and irinotecan dose reduction) were more frequent than oxaliplatin dose reduction. *See* Ex. 2043 (Gunturu) at 3. In my opinion, a POSA would understand preemptive oxaliplatin dose reduction to be among the less frequently practiced FOLFIRINOX modifications.

259. Finally, Dr. Ratain identifies no support for the proposition that a POSA would have been motivated to specifically pursue 60 mg/m². As discussed *supra*, the Conroy references do not teach preemptive oxaliplatin dose reduction (i.e., in the first cycle of treatment), much less to 60 mg/m².

260. Dr. Ratain opines that a POSA would have been motivated to select a dose of oxaliplatin that “had already been used or tested,” pointing to both Masi and Cantore in support of selecting a 60 mg/m² oxaliplatin dose. Ex. 1002 at ¶ 242. As Dr. Ratain agreed during his deposition, Masi does not disclose the use of a 60 mg/m² dose of oxaliplatin at all. Ex. 2073 at 102:25-103:3. And, Dr. Ratain ignores that Cantore is silent on any treatment that includes—as the claimed methods do—liposomal irinotecan, 5-FU, or LV, at any dose(s). Cantore instead describes a two-drug combination that includes 60 mg/m² oxaliplatin but—far from teaching the claimed dose—concludes that “higher doses” should be studied. *See* Ex. 1009 at 5

(“Future studies should try *higher doses* of irinotecan and *oxaliplatin* in patients.”) (emphasis added); *see also supra* at ¶¶ 193-200.

261. To the extent other references describe oxaliplatin dose reduction in the first cycle of treatment, they do not motivate a POSA to pursue 60 mg/m². *See, e.g.*, Ex. 2050 (Li) (starting dose of 68 mg/m²); Ex. 2052 (Wang) (starting dose of 65 mg/m²); Ex. 2054 (Wei) (starting dose of 72.25 mg/m²); Ex. 2062 (Kang) (starting dose of 63.75 mg/m²); Ex. 2064 (Eraslan) (starting dose of 65 mg/m²); Ex. 2071 (Zhou) (starting dose of 65 mg/m²). Even if the prior art provided motivation to preemptively reduce the dose of oxaliplatin in FOLFIRINOX (it does not), a POSA would not be motivated to pursue 60 mg/m².

(iii) A POSA Would Have Been Aware of Multiple Different Approaches for Addressing Toxicity Concerns, None of Which Lead to the Claimed Methods

262. In my opinion, a POSA would have been aware of a variety of approaches that had already been employed to address toxicity issues with FOLFIRINOX. *See supra* at ¶¶ 56-63. A POSA would not have been motivated therefore to make the four precise modifications proposed by Dr. Ratain. The art as a whole taught modifications other than removing the 5-FU bolus and preemptive dose reduction reported to address toxicity issues. Dr. Ratain ignores those other approaches.

263. For one, a POSA would not undertake modifications to FOLFIRINOX lightly, given this particular field of treatment. Patients with metastatic pancreatic cancer are at an advanced stage of the disease. As such, the goal of first-line therapy is to administer the most effective dose that a patient can tolerate. *See supra* ¶ 50. Because dose reduction may compromise efficacy, a POSA would not undertake dose reduction without a strong rationale for doing so. *Id.*

264. Consistent with this, the prior art reflects a variety of FOLFIRINOX modifications, for example dose reduction of a single component (e.g., the 5-FU bolus). *See* Appx. B. And in many cases, the dose reductions are for particular patient populations.¹⁴ For that reason, a POSA would not readily depart from

¹⁴ *See e.g.*, Ex. 2046 (Vasile) at 1 (Vasile “enrolled patients with cytological or histological diagnosis of pancreatic adenocarcinoma, stage III locally advanced disease without evidence of metastatic disease, [and] ECOG performance status (PS) 0 or 1, age 18-75.”); Ex. 2051 (Ozaka) at 2 (Ozaka had extensive inclusion criteria which included “histologically or cytologically confirmed pancreatic adenocarcinoma or adenosquamous carcinoma; an [ECOG] PS of 0 or 1; age 20–75 years; MPC with at least one measurable lesion; and adequate haematological, liver, and renal function [specifically defined]. Patients were excluded if they had the following: prior chemotherapy or radiation therapy; grade 2 or higher peripheral sensory neuropathy; blood transfusion, blood products, or haematopoietic growth factor preparations such as G-CSF within 7 days before enrolment; UGT genetic polymorphisms of homozygous UGT1A1*28 or UGT1A1*6 or heterozygous UGT1A1*6 and UGT1A1*28; apparent coelomic fluid (pleural effusion, ascites, or pericardial fluid) or peritoneal cancer dissemination; diarrhoea including watery stools within 3 days before enrolment; poorly controlled diabetes; synchronous or metachronous double cancer, excluding carcinoma in situ or intramucosal carcinoma cured by local treatment; active infection; or other serious concomitant diseases.”).

FOLFIRINOX modifications that were already known and associated with clinical data in the available literature.

265. A POSA would have been aware of a variety of different FOLFIRINOX modifications for addressing toxicity concerns that were different than the four simultaneous modifications proposed. *See id.* As I mentioned already, some of these approaches entailed removal of the 5-FU bolus, while others reduced the 5-FU bolus dose. *See id.* Other approaches removed or reduced the 5-FU bolus dose in combination with irinotecan dose reduction. *See id.* Other approaches reduced dosages of all components. *See id.* Notably, 5-FU bolus removal in combination with oxaliplatin dose reduction (two of Dr. Ratain's proposed modifications) is not mentioned (or otherwise prevalent) in the literature. *See id.* A POSA therefore would have been aware of multiple approaches for addressing FOLFIRINOX's toxicity issues, without any clear direction—or motivation—towards Dr. Ratain's urged modifications.

266. Even after the August 21, 2015 priority date, modification to the FOLFIRINOX regimen were being made. Some approaches describe removal of the 5-FU bolus in combination with irinotecan dose reduction. *See id.* Others describe dose reduction of several components. *See id.* Others describe dose reduction of a single FOLFIRINOX component. *See id.* The fact that various approaches were being pursued demonstrates lack of clear direction (or motivation)

in the art for one approach over another. In my experience, this reflects the uncertainty in the field regarding the optimal approach to modifying FOLFIRINOX to reduce toxicity while maintaining efficacy.

267. Dr. Ratain does not explain or provide any discussion as to why a POSA would have made the four, specific modifications to FOLFIRINOX over the numerous, other more limited modifications in the art. For example, Dr. Ratain does not explain why, in order to address such toxicity issues, a POSA would have removed the 5-FU bolus over other approaches for addressing toxicity concerns where the 5-FU bolus was not removed. *See id.*

268. Dr. Ratain also does not explain why, in addition to removal of the 5-FU bolus, a POSA would have been motivated to pursue further modifications, including dose reduction and of which components. For example, Dr. Ratain opines that a POSA would “have known that a modification of the 5-FU dose would also improve the toxicity profile” of FOLFIRINOX and would have been motivated to reduce the 5-FU bolus, pointing to Mahaseth in support. Ex. 1002 at ¶ 244. As I have discussed above, and as Dr. Ratain agrees, a POSA would have understood that Mahaseth’s modified regimen was “well tolerated and improved the safety profile of the original FOLFIRINOX regimen” and “maintained FOLFIRINOX’s overall efficacy.” *Id.*; *see also supra* at ¶ 165. Dr. Ratain fails to explain why a POSA

would have been then motivated to further modify the regimen in the specific ways he proposes given that Mahaseth's regimen achieved the goal of reducing toxicity.

269. In my opinion, for the reasons discussed above a POSA would not have been motivated to make all of Dr. Ratain's specific modifications, much less at the same time.

**(b) The Known Properties of Liposomal Irinotecan
Would Not Have Motivated a POSA to Pursue the
Claimed Methods**

270. Dr. Ratain opines that a POSA would have been motivated to replace irinotecan with liposomal irinotecan in the FOLFIRINOX regimen due to its purported "superiority" over free irinotecan. Ex. 1002 at ¶¶ 235-38. He relies on Ko, Saif, and Bayever in support of this opinion. None of these references, however, provide a POSA with a motivation to replace irinotecan in FOLFIRINOX with liposomal irinotecan at the claimed dose of 60 mg/m² and make the additional modifications proposed by Dr. Ratain.

271. As I explained earlier, Ko's generic suggestion that liposomal irinotecan be "explore[d]" "as part of combination regimens for APC" in "the first-line setting" (Ex. 1008 at 5) does not direct a POSA to any particular combination of drugs, much less any particular dose or regimen. *See supra* at ¶ 192. Ko does not teach or suggest replacing the irinotecan component in FOLFIRINOX with liposomal irinotecan. In fact, when referencing FOLFIRINOX, Ko instead directs a

POSA to investigate the use of liposomal irinotecan alone or in combination with gemcitabine—not in combination with oxaliplatin, 5-FU, and/or leucovorin.

272. Saif also does not provide a POSA with any clear motivation to substitute liposomal irinotecan with irinotecan. For one, as I explained previously, Saif does not disclose which dosing regimen achieved the clinical results presented therein. *See supra* at ¶ 183. Rather, it reports that a particular three-drug combination (liposomal irinotecan, fluorouracil, and leucovorin) at unknown dosages and timing or method of administration resulted in a higher overall survival in an unknown number of patients of unknown demographics given only two of those drugs (fluorouracil and leucovorin) in a similarly unknown manner. *Id.*

273. In my opinion, Saif does not suggest replacing irinotecan in FOLFIRINOX with liposomal irinotecan and certainly not at the claimed dose. Rather, Saif questions whether such a replacement is even worthwhile, given countervailing toxicity concerns. *Id.* At most, Saif is equivocal on the potential effect of a combination therapy that includes liposomal irinotecan and oxaliplatin, along with 5-FU and LV.

274. Bayever similarly does not suggest Dr. Ratain's proposed modification. As explained previously, Bayever is entirely silent on the use of liposomal irinotecan in combination with a therapy that includes oxaliplatin. *See supra* at ¶ 174. In addition, Dr. Ratain at best concludes that the art taught a POSA that liposomal

irinotecan has several attributes that “may” provide an improved therapeutic index and “could result in clinical superiority to free irinotecan.” Ex. 1002 at ¶¶ 237-38; *see also supra* at ¶ 91. Such speculative teachings based on preclinical and/or early-phase studies indicates that even Bayever considered such conclusions to be hypotheses that would need to be tested, not known facts that would motivate immediate substitution into a different, more complex regimen. *Id.*

275. As I explained above in response to Dr. Ratain’s Section VII (E), Dr. Ratain only draws a conclusion of purported “superiority” of liposomal irinotecan to free irinotecan in pointing to preclinical studies of liposomal irinotecan. *See supra* at ¶¶ 90-99. For the reasons I already discussed above, Dr. Ratain’s relied-upon references do not support a POSA making his proposed modifications. *Id.* None of those preclinical studies demonstrate that liposomal irinotecan would be clinically superior to irinotecan in patients for the treatment of metastatic cancer. That is because, as of the filing of the ’552 Patent, liposomal irinotecan (alone or in combination with other agents) had not been evaluated compared to free irinotecan (alone or in combination with other agents). Roy is the only reference that comes close to any such comparison; however, Roy does not support clinical “superiority” of liposomal irinotecan over free irinotecan. *See supra* at ¶ 95. Rather, Roy concludes that liposomal irinotecan had “comparable” efficacy and states that given

the limitations of the study, “a significant conclusion cannot be made from these data at this time.” *Id.* (quoting Ex. 1055 at 6).

276. As of August 21, 2015, a POSA would not have known how liposomal irinotecan would have performed in comparison with free irinotecan in a clinical study for the treatment of metastatic pancreatic cancer. Therefore, a POSA would not have been motivated to make replace liposomal irinotecan along with the other three proposed modifications.

277. Moreover, a POSA would have understood that the combination of irinotecan and oxaliplatin presents a heightened risk of neutropenia in patients. A POSA therefore may have been dissuaded from combining liposomal irinotecan with oxaliplatin.

278. A POSA would have understood that neutropenia is a serious, dose-limiting side effect that is associated with irinotecan. Ex. 1054 at 6 (identifying neutropenia as a “severe irinotecan-associated toxicity”). The FDA-approved labeling for Camptosar (irinotecan) reports neutropenia among “[t]he most clinically significant adverse events for patients receiving irinotecan-based therapy.” Ex. 2074 (Camptosar 2014 Label) at 14. A POSA would have further understood that oxaliplatin is also associated with risk of neutropenia. Ex. 1038 at 1 (identifying neutropenia as among the most common adverse events associated with oxaliplatin).

279. A POSA would further appreciate that the combination regimen of FOLFIRINOX, which contains both irinotecan and oxaliplatin, presents risk of neutropenia. For example, Conroy reports neutropenia as the most common grade 3 or 4 adverse event in the study. *See* Ex. 1003 at 8, Table 3. And upon the first occurrence, the protocol was to reduce the dose of irinotecan, not oxaliplatin. *See* Ex. 1004 at 16. This reflects the understanding that irinotecan was the primary driver of this particular toxicity.

280. Conroy reports further that of the two patients who died from treatment-related causes in the study, one died from febrile neutropenia. Ex. 1003 at 6. Conroy 2013 also reports that, “[n]ot surprisingly,” patients in the FOLFIRINOX arm of the Conroy study experienced “significantly higher rates of grade 3-4 neutropenia (45.7 % versus 21 %)” than patients in the gemcitabine arm. Ex. 1041 at 3. A POSA would have been cautious, due to the overlapping risk of neutropenia, to substitute liposomal irinotecan into FOLFIRINOX.

281. To the extent that Dr. Ratain argues that the toxic properties of irinotecan would have prompted a POSA to replace irinotecan with liposomal irinotecan, the prior art taught dose reduction as a way of addressing that problem. And in any event, Dr. Ratain fails to explain why a POSA would be motivated to do this in addition to all of the other modifications necessary to arrive at the claimed invention.

(c) A POSA Would Not Have Been Motivated to Select 60 mg/m² Dose of Liposomal Irinotecan

282. Dr. Ratain opines that “[a] POSA would have found any dose within 60-80 mg/m² an obvious option for future study” and would have “certainly considered a starting dose of 60 mg/m² as taught by Bayever.” Ex. 1002 at ¶ 240. As I explained previously, Bayever does not disclose a treatment regimen of liposomal irinotecan in combination with oxaliplatin and does not discuss the use of liposomal irinotecan as part of the FOLFIRINOX regimen. *See supra* at ¶ 174. Therefore, a POSA would not have an understanding as to what dose of liposomal irinotecan to use in such a regimen.

283. Bayever also does not teach a POSA to use a 60-80 mg/m² dose of liposomal irinotecan in a combination treatment with oxaliplatin. Rather, Bayever discloses the use of doses of 120 mg/m² every three weeks or 80 mg/m² every two weeks for patients that are not homozygous for UGT1A1*28. *See supra* at ¶ 179. Bayever discloses dose reductions in patients in the event of certain toxicities including reduction of the liposomal irinotecan dose to 50 mg/m² **and lower** in the event of certain hematological toxicities and diarrhea. *Id.* Bayever also teaches that patients homozygous for UGT1A1*28 that receive liposomal irinotecan in combination with 5-FU and leucovorin should receive an initial dose of 60 mg/m² liposomal irinotecan, but directs the dose of liposomal irinotecan be increased to 80 mg/m² if the patient does not experience any drug related toxicity after the first

administration. *Id.* Thus, to the extent that patients homozygous for UGT1A1*28 receive an initial dose of 60 mg/m², the study protocol instructs dose escalation—not dose reduction—in the absence of toxicity.

284. Bayever does not set forth any Phase III clinical results for the doses discussed therein, and Saif does not provide a POSA information as to which dosing regimen achieved the results discussed therein. *See supra* at ¶ 183. Therefore, given that none of these doses in Bayever are contemplated as part of a regimen with oxaliplatin, a POSA would not have had a motivation to select any particular dose, much less with a reasonable expectation of success.

285. Other references disclose higher doses of liposomal irinotecan. *See, e.g.,* Ex. 1057 at 2 (Chen recommends 120 mg/m² every three weeks, a higher weekly dose than claimed, “for future phase II studies”); Ex. 1055 at 2 (patients in the liposomal irinotecan arm received 120 mg/m² every three weeks). Dr. Ratain does not explain why a POSA would not consider such higher doses.

286. In addition, Dr. Ratain’s references do not provide or remotely discuss any correlation between the dose of irinotecan in FOLFIRINOX to a hypothetical dose of liposomal irinotecan in FOLFIRINOX. Instead, the art suggests that a POSA may face difficulties in attempting to make such correlation. For example, the ’209 Application states that such “quantitative comparisons are difficult” between irinotecan and liposomal irinotecan. *See* Ex. 1015 at 52 (“The comparison is

qualitative, as both irinotecan and nal-IRI have been used in different doses and schedules as monotherapy and combination therapy with other therapeutic agents; therefore quantitative comparisons are difficult.”).

287. Kim also identifies challenges in relating pharmacokinetic data to appropriate dosing. Kim states that the data reported therein “reveals the limit of relating simple AUC based exposure to in vivo tumor response.” Ex. 1058 at 1. Kim also notes that differences between mice and humans present confounding factors when relying on animal studies to predict human response. Ex. 1058 at 2 (“Identifying the source of intratumoral SN38 is confounded by the fact that the mouse species has additional carboxylesterase (CES) that can convert irinotecan to SN38 in serum.”). *See also supra* at ¶ 98. Even if motivated to incorporate liposomal irinotecan into an existing therapy, a POSA would understand the challenges in arriving at an appropriate dose.

**(d) A POSA Would Not Reasonably Expect That Its
Multiple, Specific FOLFIRINOX Modifications
Would Achieve the Claimed Invention**

288. As I stated above, a POSA would not have combined multiple modifications to an established treatment regimen without sequential testing to evaluate each change independently. *See supra* at ¶¶ 231-233. The FOLFIRINOX regimen was a well-established, four-drug combination with known efficacy and a defined toxicity profile. Replacing one component of this complex regimen with a

novel drug while simultaneously maintaining or adjusting other components would not have provided a POSA with a reasonable expectation of success.

289. When modifying complex multi-drug regimens, pharmaceutical development follows an iterative approach: test one modification, evaluate the results, then proceed to the next modification. A POSA would not simultaneously replace irinotecan with liposomal irinotecan and adjust dosing of other agents without first understanding how the liposomal formulation performs in isolation or in simpler combinations.

290. The FOLFIRINOX regimen represents a carefully calibrated combination where each component contributes to both efficacy and toxicity. Substituting liposomal irinotecan—which has different pharmacokinetic properties, including a 2-3 fold longer half-life and 20-fold increase in tumor SN-38 exposure compared to free irinotecan (Ex. 1006 at 20-21)—could alter this balance in unpredictable ways. A POSA would recognize that such a substitution could interact with oxaliplatin, 5-FU, and leucovorin in unknown ways, potentially creating unanticipated toxicities or reducing efficacy in patients. A POSA would also understand that the interaction between the drugs can result in variable responses among patients that render the outcome of multiple changes unpredictable. A POSA therefore would not understand dose reduction, for example of oxaliplatin, in one regimen to behave the same way in a different regimen.

291. Moreover, a POSA would not have considered dose adjustment in this context to be “routine experimentation” or “routine optimization” as suggested by Dr. Ratain. Rather, a POSA would not have undertaken new modifications to FOLFIRINOX without a rational basis for doing so. For example, a POSA would have known that preemptive dose reduction, or dose reduction of the starting dose that has already demonstrated efficacy may negatively compromise treatment outcomes. Ex. 1052 at 2 (“Dose reductions used as a means of reducing toxicity may undermine outcomes when $\leq 85\%$ of the standard dose intensity is delivered.”). A POSA therefore would not consider dose modification to be a matter of “routine optimization.” Indeed, a POSA would not necessarily preemptively reduce doses given the potential impact on efficacy.

292. Dr. Ratain also ignores the unpredictable nature of clinical effects at a given dose for oncology drugs, much less when given in combination. For example, Undevia, co-authored by Dr. Ratain, states that: “[a]nticancer drugs can have considerable interindividual pharmacokinetic variability, which, given the narrow therapeutic index of the drugs, results in *unpredictable clinical effects*.” Ex. 2023 at 2 (emphasis added); *see also* Ex. 2026 at 1 (“[C]ombination therapy in oncology patients makes establishing relationships between drug concentration and therapeutic end points difficult.”). Further, “the behaviour of drugs with non-linear pharmacokinetics is not as predictable as that of drugs with linear

pharmacokinetics.” Ex. 2023 at 4. At least one of the drugs in the claimed combination therapy, 5-FU, exhibits non-linear pharmacokinetics. *Id.* Despite this recognition, Dr. Ratain did not consider whether any of the drugs at issue here exhibit non-linear pharmacokinetics. Ex. 2073 at 125:9-126:10.

293. A POSA would likewise appreciate the lack of predictable dose-effect relationship in this particular area of treatment. For example, Bayever acknowledges that there are “marked heterogeneities in efficacy and toxicity observed clinically.” Ex. 1006 at 3; *see also id.* at 10-12 (further describing heterogeneity in pharmacogenetics); *see also* Ex. 2026 at 1 (“[T]he degree of interpatient variation in clinical outcomes following standard doses of chemotherapy is large and plasma concentration of cytotoxic drugs may vary up to 14-fold or even 100-fold in the case of 5-fluorouracil.”). A POSA would understand that the dose-effect relationship of liposomal irinotecan is unpredictable for at least the reason of such variability in the patient population.

**(e) A POSA Would Not Reasonably Expect Success
Based on Preclinical or Early-Phase Data on
Liposomal Irinotecan**

294. Dr. Ratain opines that, “even if the claimed regimen were deemed to be in some way superior to the closest prior art (FOLFIRINOX . . .), a POSA would not have found that result to have been unexpected” in light of Bayever, Ko, and Saif. Ex. 1002 at ¶ 261. I disagree.

295. As I explained previously, Bayever does not discuss the use of liposomal irinotecan with oxaliplatin. Therefore, a POSA would not have had any expectation as to whether a combination of the two would achieve Dr. Ratain's stated goals of reduced toxicity and superior efficacy. Furthermore, Bayever only sets forth preclinical data or early-phase clinical data with respect to the "superior" properties of liposomal irinotecan in comparison with irinotecan. The data from these studies might inform an appropriate dose for further study, however, for at least the reasons I have already discussed above, a POSA would not have had a reasonable expectation of success based on such data. *See supra* at ¶¶ 90-99.

296. A POSA would have also understood that preclinical and early-phase data (such as that in Bayever) is of limited predictive value in the particular field when adding an additional drug such as oxaliplatin. Dr. Ratain's own references support this. For example, Kim indicates that animal models are not necessarily predictive of dosing in humans. *See, e.g.*, Ex. 1058 at 1 (describing the "limit of relating simple AUC based exposure to in vivo tumor response"). Hann also describes that "[e]fforts to treat pancrea[ti]c cancer have been hampered by a lack of effective therapeutic options as well as predictive preclinical models." Ex. 1059 at 1. Therefore, the preclinical animal data presented in Bayever would have been of limited predictive value to a POSA to the presently claimed invention.

297. Additional literature also support this position. For example, a study of clinical development success rates from 2006 to 2015 reports that, of all disease areas, oncology had the lowest likelihood of approval (5.1%) from Phase I. Ex. 2008 (BIO study) at 3. And, within oncology, the Phase III failure rate for new pancreatic cancer treatments is the highest. *See* Ex. 2009 (Thota) at 4 (“The failure rate of phase III clinical trials in advanced pancreatic cancer is high (87%).”); *see also* Ex. 2008 (BIO study) at 15 (“Solid tumor drugs for pancreatic cancer seemed to have the toughest challenges in Phase III studies (13.1%, n=15).”); Ex. 2044 (Amiri-Kordestani) at 2 (“[I]n cancer drug development, reality is all too often failure.”); Ex. 2045 (Booth) at 1 (“The dramatic unpredictability of single-arm, uncontrolled Phase II trials in cancer helps explain why anti-cancer drug development is so challenging.”).

298. Dr. Ratain’s own publications recognize the low predictive value of preclinical and/or early-stage data. Paller (Ex. 1045), a reference co-authored by Dr. Ratain, explicitly states that “[t]he level of preclinical data required to predict a benefit in clinical trials is currently unknown, because preclinical studies do not generally predict success of clinical trials.” *See* Ex. 1045 at 2. Hamberg (Ex. 1046), another reference co-authored by Dr. Ratain, also acknowledges the complexities and challenges specifically associated with early-stage trials of combination therapies. *See* Ex. 1046 at 9 (“Combination phase I studies are extremely

complex.”); *see also* Ex. 1045 at 2 (“The design and conduct of the phase I combination trial present specific challenges, such as the optimum selection of agents to combine among the range of possible combinations; the selection of the appropriate dose and schedule (including which drug or drugs to dose escalate); drug-drug interactions; overlapping toxicities; and logistical and regulatory challenges.”).

299. Another of Dr. Ratain’s publications states that “it is clear that phase II oncology trials have a high negative predictive value but a *low positive predictive value*,” where “[p]ositive predictive value is the likelihood of approval (for a disease) given a positive phase II trial (i.e., exceeding threshold response rate).” Ex. 2010 (Ratain 2005) at 1 (emphasis added); *see also* Ex. 2007 (Valsecchi) at 6-8 (discussing negative trials—a biological rationale for further study does not equate to a reasonable expectation of success). These references undermine reliance on Bayever’s data for a reasonable expectation of success.

300. A POSA would have also been aware of the unpredictability associated with new combination therapies comprised of multiple cytotoxic agents. For example, as I mentioned above, a POSA would understand that liposomal irinotecan and oxaliplatin are each very toxic, and that their combination may pose new toxicity issues that might outweigh any potential benefit of their combination. A POSA

therefore would not reasonably expect success in achieving a combination therapy that provide more than a *de minimis* therapeutic benefit.

301. Saif explicitly contemplates whether introducing liposomal irinotecan to the FOLFIRINOX regimen is “worth” the attendant toxicity concerns. Ex. 1007 at 1 (“However bone marrow toxicity has to be borne in mind.”). Similarly, Masi states that the question of whether the synergistic interactions among SN-38 (the active metabolite of irinotecan), oxaliplatin, and 5-FU will “allow[] their administration at optimal doses” was undetermined. Ex. 1012 at 2. Ko also questions whether dosing of new combination therapies will be reduced to the extent that efficacy is compromised. *See* Ex. 1008 at 4-5. Indeed, Dr. Ratain himself states that, at best, such teachings only provide a POSA with “hope[] of improving the overall survival of patients with pancreatic cancer.” Ex. 1002 at ¶ 261. My understanding is that “hope” does not rise to the level of reasonable expectation of success.

302. A POSA also would have been aware that combination therapies in the treatment of metastatic pancreatic cancer have failed. For instance, Gunturu describes that, “[d]espite promising phase II trials with gemcitabine-based combinations in advanced pancreatic cancer, the addition of cytotoxic drugs (e.g., FU, capecitabine, oxaliplatin, cisplatin, irinotecan) or targeted agents . . . to gemcitabine has yielded no meaningful gains in overall survival in multiple

randomized trials comparing gemcitabine doublets to gemcitabine alone, till recently.” Ex. 2043 at 1. A POSA would have likewise been aware of the failure of such combination therapies.

(f) Unexpected Results Support Non-Obviousness

303. The clinical trials of NALIRIFOX support the unexpected results of that regimen over FOLFIRINOX.

304. Wainberg demonstrated clinically meaningful efficacy results. Wainberg presents results from a Phase I/II study of NALIRIFOX in 32 treatment-naïve patients with locally advanced or metastatic pancreatic cancer. *See* Ex. 1018; Ex. 1019. It showed that the NALIRIFOX regimen achieved: (1) median PFS of 9.2 months (95% CI: 7.69-11.96)—substantially longer than typical second-line therapies and comparable to first-line standards; (2) median OS of 12.6 months (95% CI: 8.74-18.69)—exceeding outcomes for many first-line regimens; (3) overall response rate of 34.4% (95% CI: 18.6-53.2%)—demonstrating meaningful tumor shrinkage; (4) disease control rate of 71.9% at 16 weeks—showing that the regimen controlled disease in the majority of patients; and (5) manageable toxicity profile—with no unexpected safety signals. Ex. 1019 at 2, 5 (Table 3), 8. These results demonstrated that the 60/60 liposomal irinotecan/oxaliplatin dose combination achieved substantial clinical activity—not merely tolerability. As explained above, and as the Patent Owner discussed during the prosecution of the ’552 Patent (and I

agree), these improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen. *See supra* at ¶¶ 120-123. A POSA could not have expected based on the prior art that this dose combination would deliver FOLFIRINOX-level efficacy with improved tolerability.

305. The Phase III NAPOLI-3 trial with NALIRIFOX affirmed these clinical benefits with the 60/60 combination. *See* Ex. 2032; *see also* Ex. 1011. For example, in the NAPOLI-3 trial, NALIRIFOX demonstrated superior efficacy to the combination regimen of gemcitabine + nab-paclitaxel, with improvement in overall survival and acceptable toxicity. Indirectly, these results also demonstrate comparable efficacy to FOLFIRINOX while delivering substantially improved tolerability. Specifically, the NAPOLI-3 trial demonstrated that NALIRIFOX achieved a median OS of 11.1 months (identical to FOLFIRINOX in PRODIGE-4); a median PFS of 7.4 months (superior to FOLFIRINOX's 6.4 months); and a ORR of 41.8% (superior to FOLFIRINOX's 31.6%). Ex. 1011 at 2 (Table 1). NALIRIFOX achieved improved toxicity results in that it had grade ≥ 3 peripheral neuropathy of only 6.5% (compared to 9% with FOLFIRINOX); neutropenia/febrile neutropenia of 24%/2% (compared to 46%/5% with FOLFIRINOX); and grade ≥ 3 diarrhea of 20% (compared to 13% with FOLFIRINOX, though still improved overall tolerability). *Id.*

306. A POSA would recognize that achieving therapeutic equivalence with meaningfully improved tolerability represents a qualitative, not merely quantitative, advance in cancer treatment. This is particularly true in metastatic pancreatic cancer, where patients who can tolerate therapy longer derive greater clinical benefit, where quality of life is paramount. In a disease with median survival measured in months, reducing debilitating side effects while maintaining efficacy fundamentally changes the risk-benefit calculus. *See, e.g.*, Ex. 2029 (stating that “NALIRIFOX is associated with improvement in PFS and QALY [(Quality Adjusted Life Year)]” and “[t]he analysis highlights the importance of AE management for improving quality of life and cost in the recipients of FOLFIRINOX”); Ex. 2030 (Xiang).

307. The challenge of treatment is to administer the most effective regimen while avoiding toxicity issues that may require discontinuation of treatment or otherwise compromise efficacy of the most effective dose. In this field, an improvement in overall survival by weeks can be significant. Advances in treatment for metastatic pancreatic cancer have involved improvement in survival on that order.

308. A POSA would have expected that reducing oxaliplatin from 85 mg/m² to 60 mg/m² would reduce toxicity, but would also have expected a corresponding reduction in efficacy. Clinical evidence confirms this expectation. For example, a 2025 real-world study showed that mFFX—a dose-reduced version of

FOLFIRINOX for improved tolerability—achieved only 8.6 months median OS, substantially lower than both FOLFIRINOX (11.1 months in PRODIGE-4) and NALIRIFOX (11.1 months in NAPOLI-3). *See* Ex. 2031 (Cockrum). In addition, two 2024 randomized trials specifically tested modified FOLFIRINOX efficacy over gemcitabine/nab-paclitaxel. *See* Ex. 2033 (Skorupan). One found gemcitabine to be superior to mFFX and the other closed early for futility and therefore, could not demonstrate superiority. *Id.* at 3. The unexpected result is that NALIRIFOX broke this paradigm: it achieved improved tolerability without sacrificing efficacy. This was not predictable from the prior art’s teachings about dose-toxicity relationships.

309. Post-priority date studies have suggested that NALIRIFOX has better efficacy and tolerability than gemcitabine/nab-paclitaxel and FOLFIRINOX does not. *See* Ex. 2033; Ex. 2034. For example, NALIRIFOX demonstrated superiority over GnP in NAPOLI-3, while mFFX failed to show superiority over GnP in two randomized trials that specifically tested modified FOLFIRINOX over gemcitabine/nab-paclitaxel. *See* Ex. 2033 at 2-3; Ex. 2034. This indirect comparison suggests that NALIRIFOX achieved what dose-modified FOLFIRINOX could not—maintaining or improving upon the full efficacy of the original FOLFIRINOX regimen while improving tolerability. While Skorupan acknowledges that a head-to-head trial would be needed for definitive proof (Ex. 2033 at 1-2), this pattern of results supports the conclusion that NALIRIFOX’s

combination of comparable efficacy with improved safety represents an unexpected advance beyond what dose modifications to FOLFIRINOX achieved. *See* Ex. 2034 (reporting that superiority of mFFX over gemcitabine/nab-paclitaxel was not demonstrated).

310. Dr. Ratain dismisses the toxicity improvement of NALIRIFOX over FOLFIRINOX as “clinically insignificant,” based on Nevala-Plagemann (Ex. 1002 at ¶ 260), but this characterization misrepresents both the data and clinical reality. That reference states that NALIRIFOX had a reduction in neutropenia from 46% to 24% and a reduction in febrile neutropenia from 5% to 2%. Ex. 1011 at 2. This translates to fewer hospitalizations, reduced infection risk, and improved treatment adherence. While Nevala-Plagemann states that the reduction in peripheral neuropathy was “clinically insignificant” (*id.*), I disagree given that peripheral neuropathy profoundly impacts quality of life and such a reduction also allows patients to continue treatment for longer. A POSA would understand that these improvements, achieved while maintaining efficacy, represent a fundamental therapeutic advance—not an expected incremental change.

311. Dr. Ratain also opines that Nichetti’s meta-analysis and Nevala-Plagemann’s commentary “clearly refute” unexpected results because they found no significant OS difference between NALIRIFOX and FOLFIRINOX. Ex. 1002 at ¶ 260. I disagree for the reasons discussed above. As of August 21, 2015, a POSA

would not have expected achieving comparable efficacy with FOLFIRINOX while delivering a more tolerable regimen. In addition, Dr. Ratain ignores that Nevala-Plagemann acknowledges NALIRIFOX demonstrated “modest improvement” in OS over gemcitabine/nab-paclitaxel in NAPOLI-3 (Ex. 1011 at 1), which was sufficient for FDA approval.

312. Moreover, to the extent that the findings of Nichetti suggest comparative efficacy between NALIRIFOX and FOLFIRINOX, they also indicate differences in toxicity. *See* Ex. 1010 at 9. Nichetti concludes, at most, that its findings “may empower a more careful evaluation of these regimens.” Ex. 1010 at 10. Nevala-Plagemann is an opinion piece that purports to compare data from different clinical studies. *See* Ex. 1011. At most, Nevala-Plagemann purports to identify issues for future consideration and study. *See id.* at 2 (concluding that further research is needed to assess the benefit of NALIRIFOX over existing treatment options). Neither Nichetti nor Nevala-Plagemann establishes that NALIRIFOX and FOLFIRINOX are “identical” in efficacy, or in any other respect.

* * *

313. For the reasons discussed above, it is my opinion that claim 1 of the ’552 Patent is not obvious over Dr. Ratain’s relied-upon art.

314. The remaining claims asserted by CSPC and Dr. Ratain in Ground 1 (claims 3-6 and 8-14) are all non-obvious for all the reasons discussed above with

respect to claim 1. Claims 3-6, 8-11, and 13 all depend from claim 1 and thus contain the same limitations as claim 1 which are non-obvious for the reasons described *supra*. Claim 12 is an independent claim requiring the same administration of the same four-drug combination in the same amounts as in claim 1, differing only in that the patients in claim 12 have not previously received “gemcitabine” specifically, as compared to claim 1’s requirement that the patients have not previously received “an antineoplastic agent.” *See* Ex. 1001 at 46:63-48:42. Thus claim 12 (and claim 14 which depends from claim 12) is also non-obvious for the same reasons discussed above with respect to claim 1.

B. Ground 2: The Prior Art Disclosed in Ground 1 in Combination with Masi and Ginocchi Does Not Render Obvious Claims 2, 7, or 15

315. Dr. Ratain’s heading states that “[c]laims 7 and 15 would have been obvious in view of the prior art disclosed in Ground 1 in further view of Masi and Ginocchi.” Ex. 1002 at 120 (*see* Heading “B”). Dr. Ratain, however, has not set forth any opinions in this section how claims 7 and 15 are obvious in further view of Masi and Ginocchi. In fact, he does not rely on or cite to either of those references in this section of his expert declaration. Dr. Ratain then states, “[i]n 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.” *Id.* at ¶ 308. Dr. Ratain, however, did not present any opinions with respect to claim 2 of the ’552 Patent. In the event

that Dr. Ratain is permitted to amend or fix these deficiencies, I reserve the right to respond accordingly.

316. It is my understanding nonetheless that CSPC argues that “Claims 2, 7, and 15 are obvious under 35 U.S.C. § 103 based on the prior art disclosed in Ground 1 in combination with Masi and Ginocchi.” Paper 1 at 58. For the reasons I state below, I disagree.

1. Claim 2

317. CSPC states that “[c]laim 2 is also obvious based on the discussion above with respect to claim 1 in Ground 1 and the fact that Bayever discloses that liposomal irinotecan MM-398 should be administered first before any other drugs, and that Masi discloses that irinotecan should be administered prior to oxaliplatin in chemotherapy treatment for metastatic colorectal cancer based on the FOLFOXIRI regimen.” Paper 1 at 58.

318. First, as I mentioned above, Dr. Ratain’s expert declaration is devoid of any opinions with respect to claim 2 at all, much less in the context of Ground 1. In addition, CSPC does not set forth any arguments with respect to the purported obviousness of claim 2 in the context of Ground 1. Therefore, I do not understand how CSPC concludes that “[c]laim 2 is *also* obvious based on the discussion above.” Regardless, for the reasons I have already discussed above in Ground 1, claim 1 of

the '552 Patent is not obvious in light of the prior art relied upon by Dr. Ratain and/or CSPC.

319. Beyond this threshold problem, the substantive arguments regarding claim 2 fail because the prior art does not teach or suggest the specific sequence recited in the claim. Claim 2 requires that “each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.” Ex. 1001 at 47:10-12. None of the references relied upon by CSPC—whether individually or in combination—discloses this timing requirement. More fundamentally, none teaches administering liposomal irinotecan before oxaliplatin.

320. The timing and sequence of drug administration in combination chemotherapy is not a trivial matter. In my clinical experience, the order in which chemotherapeutic agents are given can affect both the efficacy of treatment and the toxicity profile. These effects can arise from pharmacokinetic interactions, pharmacodynamic interactions, or impacts on drug metabolism. The specific 2-hour interval between completion of liposomal irinotecan infusion and initiation of oxaliplatin represents a deliberate clinical choice, not merely “routine optimization” as CSPC and Dr. Ratain suggest (*see* Paper 1 at 59).

321. Conroy explicitly teaches administering oxaliplatin before irinotecan. The FOLFIRINOX regimen described in Conroy consists of “oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately

followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector.” Ex. 1003 at 3. This teaching is different from the claim 2 requirement that liposomal irinotecan administration begins before the start of oxaliplatin administration. A POSA reading Conroy would understand that the established practice for treating metastatic pancreatic cancer with this drug combination involved administering oxaliplatin first, not liposomal irinotecan.

322. When the standard of care clearly establishes a particular sequence of administration for treating a specific disease, a POSA would need some teaching or motivation in the prior art to depart from that sequence. CSPC has not identified any such teaching or motivation. Simply asserting that a different sequence would have been “obvious” ignores the reality that the established standard of care strongly influences clinical practice and a POSA’s expectations.

323. CSPC points to Bayever’s alleged teaching that “liposomal irinotecan MM-398 should be the first drug administered in therapy.” Paper 1 at 59 (citing Ex. 1006 at claim 4). However, CSPC cites only claim 4 of Bayever, which recites: “[t]he method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.” Ex. 1006 at 54. This claim describes a three-drug combination consisting

of liposomal irinotecan, leucovorin, and 5-FU. It says nothing about oxaliplatin because oxaliplatin is not part of this particular combination. A POSA would not extrapolate from Bayever's teaching regarding the sequence of three drugs (none of which is oxaliplatin) to determine the appropriate sequence when a fourth drug—oxaliplatin—is added to the regimen. The pharmacology and clinical considerations change when additional agents are introduced into a combination therapy.

324. Regarding Masi, this reference describes treatment of metastatic colorectal cancer, not pancreatic cancer. Ex. 1012 at 1. In my experience, the biology of colorectal cancer differs substantially from that of pancreatic cancer. Treatment regimens that are effective in one cancer type do not necessarily transfer to another. A POSA would exercise caution in applying teachings from colorectal cancer studies to pancreatic cancer patients.

325. Even setting aside the different disease context, Masi has several limitations that prevent it from teaching what claim 2 requires. First, Masi discusses conventional irinotecan, not liposomal irinotecan. As I have explained throughout this declaration, liposomal irinotecan has distinctly different pharmacokinetic properties compared to conventional irinotecan—including prolonged circulation time, altered distribution, and different release kinetics. *See supra* at ¶¶ 94, 97, 99. The sequence of administration appropriate for conventional irinotecan cannot

simply be assumed to apply to liposomal irinotecan without consideration of these differences.

326. Second, Masi's rationale for its particular administration sequence was based on *in vitro* studies using "two human colon cancer cell lines" showing that "synergy occurs only when irinotecan precedes oxaliplatin/5-FU exposure." Ex. 1012 at 5. These were colon cancer cell lines studied under controlled laboratory conditions. A POSA would recognize that *in vitro* findings in colon cancer cells do not necessarily predict clinical outcomes in pancreatic cancer patients. The cellular mechanisms, tumor microenvironment, and drug sensitivities differ between these cancer types. It would not be appropriate to directly apply sequence-dependent synergy findings from colon cancer cell line studies to the treatment of human pancreatic cancer.

327. Third, from a chronological standpoint, Masi was published in 2004, more than six years before Conroy established FOLFIRINOX as the first-line standard for metastatic pancreatic cancer in 2011. Once Conroy demonstrated the efficacy of FOLFIRINOX with its specific administration sequence for pancreatic cancer, that became the relevant benchmark. A POSA considering how to modify FOLFIRINOX would look to more recent, disease-specific evidence rather than older studies in different cancers. The field had moved forward, and Conroy's

specific protocol for pancreatic cancer represented the current standard of care that a POSA would consider.

328. CSPC also relies on Ginocchi, but this reference likewise does not teach the claimed sequence. Ginocchi describes a modified FOLFIRINOX regimen tested in pancreatic cancer patients, but the abstract provides no detail regarding the order in which drugs were administered. Ex. 1016 at 1. The reference states only that the regimen “included a lower dose of irinotecan (administered at 150 mg/sqm on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/sqm administered as a 48-hour continuous infusion on days 1 to 3 every 14 days)” and that “[f]olinic acid and oxaliplatin remained unchanged.” *Id.* This description does not specify the sequence of administration.

329. Moreover, Ginocchi reports that the modified regimen tested was “quite well tolerated and it maintained its good activity in metastatic pancreatic cancer.” *Id.* If the modifications described in Ginocchi—reducing irinotecan dose and removing the 5-FU bolus while keeping oxaliplatin and leucovorin unchanged—successfully addressed FOLFIRINOX’s toxicity concerns while maintaining efficacy, a POSA would not have been motivated to make additional modifications. The successful result reported in Ginocchi would, if anything, discourage further tinkering with the regimen.

330. Finally, like Masi and the other references, Ginocchi discusses conventional irinotecan, not liposomal irinotecan. The reference provides no teaching about administering liposomal irinotecan in any sequence, let alone in the specific sequence and timing required by claim 2.

331. CSPC suggests that determining the precise 2-hour interval between drugs would have been “merely routine optimization.” Paper 1 at 59. I disagree with this characterization. The timing of sequential drug administration in combination chemotherapy involves careful consideration of multiple factors: the pharmacokinetics of each agent, potential drug-drug interactions, scheduling practicalities in a clinical setting, patient tolerability, and the need to maintain dose intensity. The 2-hour interval specified in claim 2—time enough to complete the liposomal irinotecan infusion and then wait before beginning oxaliplatin—is a specific clinical parameter that reflects these considerations. Dismissing such choices as “routine optimization” fails to appreciate the clinical judgment involved in designing effective and tolerable combination regimens.

2. Claim 7

332. Claim 7 depends from claim 1 and specifies that “the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.” Ex.

1001 at 47:22-25. This claim requires all four drugs to be given in this particular sequence.

333. Dr. Ratain opines that “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.” Ex. 1002 at ¶ 308. As noted, Dr. Ratain provided no analysis of claim 2 anywhere in his declaration, so this cross-reference is unhelpful. He then states that “Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen immediately following administration of leucovorin” and that “Bayever also discloses that 5-FU is administered last, immediately following administration of LV.” *Id.* at ¶ 309. He concludes by asserting that “this claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients,” citing Ginocchi. *Id.*

334. I find these arguments unpersuasive. Dr. Ratain focuses on the fact that the prior art teaches administering 5-FU last, after leucovorin. While this is true, it addresses only one portion of the claimed sequence. The more significant problem—which Dr. Ratain does not adequately address—is that the prior art teaches administering oxaliplatin before irinotecan, whereas claim 7 requires liposomal irinotecan to be administered first, before oxaliplatin.

335. Both Conroy and Mahaseth explicitly describe the FOLFIRINOX regimen as beginning with oxaliplatin administration, followed later by irinotecan.

Conroy states that FOLFIRINOX “consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin,” with irinotecan added subsequently through a Y-connector. Ex. 1003 at 3. Mahaseth similarly describes administration of oxaliplatin 85 mg/m² intravenous infusion over 2 hours, followed by leucovorin 400 mg/m² intravenous infusion over 90 minutes, and irinotecan 180 mg/m² intravenous infusion over 90 minutes. Ex. 1005 at 2. These descriptions make clear that in the established FOLFIRINOX regimen—the standard of care for first-line treatment of metastatic pancreatic cancer—oxaliplatin comes first, not irinotecan.

336. The sequence specified in claim 7 is thus fundamentally different from what Conroy and Mahaseth teach. Claim 7 requires liposomal irinotecan first, then oxaliplatin. The prior art teaches oxaliplatin first, then conventional irinotecan. This is not a minor variation; it represents a complete reversal of the order in which the platinum agent and the topoisomerase inhibitor are administered.

337. Dr. Ratain does not explain why a POSA would have been motivated to reverse this established sequence. When a particular sequence of drug administration has been validated in clinical trials and has become the standard of care, changing that sequence requires justification. There must be some reason—whether based on pharmacology, clinical experience, or other evidence—to believe

that a different sequence would be preferable or even acceptable. Dr. Ratain points to no such justification in the prior art.

338. Turning to Bayever, this reference describes a three-drug combination consisting of liposomal irinotecan, leucovorin, and 5-FU. Ex. 1006. Bayever does teach that, in this three-drug combination, liposomal irinotecan should be administered before leucovorin, and leucovorin before 5-FU. However, Bayever says nothing about oxaliplatin because oxaliplatin is not part of the regimen Bayever describes. When a fourth agent is added to a combination therapy—particularly an agent with its own toxicity profile and mechanism of action like oxaliplatin—the optimal sequence of administration may change. A POSA could not simply assume that the sequence appropriate for a three-drug regimen would remain optimal when a fourth drug is introduced.

339. Moreover, even if one were to try to integrate Bayever's three-drug sequence with a four-drug sequence, there would be no clear guidance on where oxaliplatin should fit. Bayever tells you the order for liposomal irinotecan, leucovorin, and 5-FU. But when you add oxaliplatin, should it come before the liposomal irinotecan, between the liposomal irinotecan and leucovorin, between the leucovorin and 5-FU, or after all three? Bayever provides no answer because it does not discuss oxaliplatin at all.

340. Dr. Ratain's reliance on Ginocchi and FOLFOXIRI is particularly problematic. He states that "this claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients." Ex. 1002 at ¶ 309. I am uncertain what Dr. Ratain means by "this claimed sequence" or how he concludes it matches FOLFOXIRI.

341. The FOLFOXIRI regimen, as I understand it from the prior art including Ginocchi and Masi, refers to a treatment combining FOL (folinic acid/leucovorin), F (5-fluorouracil), OX (oxaliplatin), and IRI (irinotecan). The name FOLFOXIRI itself reflects a particular history of how these regimens were developed and named in the colorectal cancer literature. However, the precise sequence of administration, the specific formulations used (conventional versus liposomal irinotecan), and the doses all matter.

342. Ginocchi's abstract does not specify the sequence in which drugs were administered. The abstract states only that the regimen "included a lower dose of irinotecan (administered at 150 mg/sqm on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/sqm administered as a 48-hour continuous infusion on days 1 to 3 every 14 days)" with "[f]olinic acid and oxaliplatin remain[ing] unchanged." Ex. 1016 at 1. From this description, I cannot determine whether irinotecan was given before or after oxaliplatin, let alone whether there was any specific timing interval between them.

343. Even if Ginocchi did use a sequence where irinotecan preceded oxaliplatin (which is not established by the abstract), that would not make claim 7 obvious. First, Ginocchi tested conventional irinotecan at 150 mg/m², not liposomal irinotecan at 60 mg/m². The pharmacokinetics are different. Second, the doses of the other components also differed from the claimed invention—Ginocchi used 2800 mg/m² of 5-FU versus the claimed 2400 mg/m². Third, Ginocchi was a single small study (39 patients) reported in abstract form. It does not represent the kind of well-established standard of care that Conroy's FOLFIRINOX represented. A POSA would not abandon the proven FOLFIRINOX sequence based on a single abstract describing a small study.

344. Most importantly, none of the references—whether Conroy, Mahaseth, Bayever, or Ginocchi—teaches a treatment regimen that consists of the four specific drugs recited in claim 1, administered in the specific sequence recited in claim 7, at the doses recited in claim 1. Conroy and Mahaseth describe FOLFIRINOX with conventional irinotecan and teach administering oxaliplatin before irinotecan. Bayever describes a three-drug combination without oxaliplatin. Ginocchi describes a modified regimen with conventional irinotecan at different doses and does not clearly specify the administration sequence.

345. The combination of references that would be necessary to arrive at claim 7—taking the four-drug combination concept from Conroy, substituting

liposomal for conventional irinotecan based on Bayever, adopting the specific doses of claim 1 (which would require further modifications), and reversing the sequence to put liposomal irinotecan first—represents a complex series of modifications. Each modification would need motivation, and collectively they would need to be compatible with maintaining both efficacy and tolerability. Dr. Ratain has not provided the analysis necessary to show that a POSA would have been motivated to make all these modifications in combination, or that a POSA would have had a reasonable expectation that doing so would result in an effective and tolerable treatment regimen.

346. For these reasons, in addition to all the reasons I discussed in Section XI (A) regarding Ground 1, claim 7 is not rendered obvious by the asserted prior art.

3. Claim 15

347. 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.” Ex. 1001 at 48:38-42.

348. Dr. Ratain argues that claim 15 is obvious for essentially the same reasons as presented for claims 1 and 2 and in further view of Bayever. Dr. Ratain conclusorily states that such administration was “known to a POSA” and “standard medical practice.” *See* Ex. 1002 at ¶¶ 310-11.

349. I disagree with Dr. Ratain's conclusory statement. While it is true that corticosteroids and anti-emetics have been used in various cancer treatment regimens, Dr. Ratain provides no analysis of whether their use would have been obvious in the specific context of the claimed four-drug combination therapy for first-line treatment of metastatic pancreatic cancer. The determination of whether to use premedication, and which specific agents to use, depends on multiple factors including the expected toxicity profile of the specific chemotherapy regimen, the patient population, and clinical experience with similar regimens. Dr. Ratain's blanket assertion that such premedication was "standard medical practice" fails to account for these nuances and does not establish that a POSA would have been motivated to include this specific premedication in the context of the claimed invention.

350. Moreover, claim 15 also requires that "each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan." As I discussed above with respect to claim 2, this sequence of administration is not taught by the prior art. Conroy teaches the opposite sequence. Bayever does not disclose a combination therapy including oxaliplatin and therefore provides no teaching regarding the sequence of administration of oxaliplatin relative to liposomal irinotecan. Masi and Ginocchi, for the reasons I have explained, do not remedy these deficiencies.

351. Therefore, even if a POSA would have known about the use of corticosteroids and anti-emetics in some cancer treatment contexts, claim 15 as a whole would not have been obvious because the prior art does not teach or suggest the specific sequence of administration recited in the claim.

352. For all these reasons, in addition to the reasons I discussed above in Section XI (A) with respect to Ground 1, claim 15 of the '552 Patent is not obvious in light of the prior art relied upon by Dr. Ratain and/or CSPC.

C. Ground 3: CSPC Fails to Show the Prior Art Disclosed in Grounds 1 and 2 in Combination with Carnevale and Dean Renders Obvious Claims 1-15

353. In my opinion, Dr. Ratain has not shown that Carnevale or Dean renders obvious claims 1-15 for at least the same reasons discussed above for Grounds 1 and 2 and for the following reasons.

354. Ground 3 represents Dr. Ratain's alternative theory of obviousness, predicated on an assumption that the '552 Patent has an effective filing date of November 10, 2017 rather than August 21, 2015. Dr. Ratain states that his Ground 3 opinions apply "if the earliest filing date of the '552 patent is November 10, 2017." Ex. 1002 at ¶ 312. As I understand from counsel, the Patent Trial and Appeal Board has already determined in its Institution Decision that the '552 Patent properly claims an effective filing date of August 21, 2015, which means that Carnevale and

Dean are not prior art because they were published after that date. Nonetheless, I will address Dr. Ratain's Ground 3 opinions.

355. Dr. Ratain's Ground 3 analysis is notably brief. For claim 1, he simply incorporates his Ground 1 analysis and adds that Dean and Carnevale "provide further motivation" to substitute liposomal irinotecan for conventional irinotecan in FOLFIRINOX. Ex. 1002 at ¶¶ 313-16. For dependent claims 3-15, he provides even less analysis—merely incorporating by reference his earlier opinions and stating that each claim is obvious "for at least the reasons set forth above." *Id.* at ¶¶ 318-30.

356. This abbreviated treatment is problematic because it fails to address the specific teachings (or lack thereof) in Carnevale and Dean, and how those references would change a POSA's understanding beyond what was already available in the Ground 1 prior art.

357. Carnevale is a review article published online in December 2015. As I discussed in Section X (I) above, Carnevale essentially summarizes clinical studies of liposomal irinotecan that had been reported by that time. The article restates the results from Ko's monotherapy study and from the NAPOLI-1 three-drug combination study (liposomal irinotecan plus 5-FU and leucovorin). Ex. 1013 at 7-8. Neither of these studies evaluated a four-drug combination including oxaliplatin, nor did they test the specific doses recited in the claimed invention.

358. Dr. Ratain relies heavily on a single sentence from Carnevale’s concluding section. He quotes Carnevale as stating 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. 1002 at ¶ 315 (quoting Ex. 1013 at 11).

359. This quotation requires context. Carnevale’s statement appears in a forward-looking section discussing potential future developments. The authors use conditional language—“would make” and “might represent”—indicating speculation about possibilities rather than established facts. This is a hypothesis, not established clinical knowledge or reasonable expectation.

360. Moreover, even this speculative statement does not suggest what doses would be appropriate for such a substitution. Carnevale provides no guidance on what dose of liposomal irinotecan should be used in FOLFIRINOX. The article also does not address whether other modifications to FOLFIRINOX—such as reducing the oxaliplatin dose or removing the 5-FU bolus—would be necessary or advisable if liposomal irinotecan were substituted for conventional irinotecan.

361. Significantly, Carnevale itself acknowledges the challenging landscape of pancreatic cancer drug development. The article states that “progress in the therapeutic development of this disease has historically taken a slow and painstaking

course, littered with numerous negative trial results.” Ex. 1013 at 1. Carnevale further characterizes pre-2010 efforts as a “stretch of failed or clinically inconsequential trials.” *Id.* at 2. In my clinical experience, this characterization accurately reflects the particularly low likelihood of success in developing new treatments for metastatic pancreatic cancer. This context of high failure rates undermines any suggestion that a POSA would have had a reasonable expectation of success in achieving an effective and tolerable modification of FOLFIRINOX through multiple simultaneous changes.

362. Dean is even less helpful to Dr. Ratain’s case. Dean is a conference abstract describing a planned Phase II clinical trial. Ex. 1014. The abstract announces that a study will compare different regimens, including one combining liposomal irinotecan with oxaliplatin, leucovorin, and 5-FU. However, Dean provides no results from this study—because the study was just beginning. The abstract reports no data on efficacy, no data on toxicity, and critically, no information about what doses of any of the components would be used.

363. Dr. Ratain states that 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.” Ex. 1002 at ¶ 314. This is misleading. Dean does not “disclose” safety or efficacy data—it merely announces a protocol to study these questions. An announcement

that a clinical trial will be conducted does not teach or suggest that the trial will be successful, nor does it provide any guidance on what doses are utilized in the proposed trial, or what outcomes to expect.

364. The distinction is critical for the obviousness analysis. A POSA in early 2016 seeing Dean's abstract would know only that researchers thought a trial of this combination was worth conducting. A POSA would not know whether the trial would succeed or fail, what toxicities might emerge, or whether the chosen doses (whatever they were) would prove optimal. In my experience, many promising trial protocols ultimately yield disappointing results, particularly in the difficult field of pancreatic cancer therapeutics.

365. Moreover, neither Carnevale nor Dean addresses a fundamental problem I have discussed throughout this declaration: how to select appropriate doses when substituting liposomal irinotecan for conventional irinotecan in a multi-drug regimen. The pharmacokinetic differences between conventional and liposomal irinotecan mean that dose equivalence is not straightforward. As I have explained, the prior art acknowledged these pharmacokinetic differences. *See supra* at ¶¶ 94, 97, 99.

366. In my opinion as a medical oncologist who treats patients with metastatic pancreatic cancer, neither Carnevale nor Dean would have provided a POSA with a reasonable expectation that the specific four-drug combination recited

in claim 1, administered at the specific doses recited in claim 1, would be effective and tolerable for first-line treatment of metastatic pancreatic cancer. The multiple simultaneous modifications required—substituting a different form of irinotecan, reducing the oxaliplatin dose, removing the 5-FU bolus, and adjusting the liposomal irinotecan dose—represent a substantial departure from the established FOLFIRINOX regimen. Success in making such modifications was not predictable based on the limited information in Carnevale and Dean.

367. Dr. Ratain provides virtually no Ground 3-specific analysis. He simply states that each claim “is obvious for at least the reasons set forth above” and incorporates his Ground 1 (and for some claims, Ground 2) analysis. Ex. 1002 at ¶¶ 318-30. Since I have explained why the Ground 1 and Ground 2 analyses are flawed, these incorporations do not salvage the Ground 3 opinions. Dr. Ratain has not explained how Carnevale or Dean specifically addresses any of the limitations recited in claims 3-15.

368. In summary, Ground 3 fails for the same fundamental reasons that Grounds 1 and 2 fail, as I have explained in Sections XI (A) and XI (B) above. Additionally, Carnevale and Dean do not remedy the deficiencies in the earlier prior art. Carnevale offers only speculation about potential future applications of liposomal irinotecan, without addressing the specific combination and doses recited in the claims. Dean announces a clinical trial protocol without providing any results

or dosing information. Neither reference bridges the gap between the prior art and the claimed invention, nor do they provide a POSA with reasonable expectation that the specifically claimed combination would be effective and tolerable.

XII. CONCLUSION

369. In signing this Declaration, I recognize 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 also recognize that I may be subject to cross-examination in the 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.

I declare under penalty of perjury under the laws of the State of New York that the foregoing is true and correct to the best of my knowledge.

Executed on this 10th day of November, 2025, at New York, NY.

Paul Oberstein

Dr. Paul E. Oberstein, M.D.

APPENDIX A

Curriculum Vitae

Paul Oberstein

Paul Eliezer Oberstein, MD, MS

Contact Information

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Cell phone: 646-599-4083
Work email address: paul.oberstein@nyulangone.org
Web page: <https://nyulangone.org/doctors/1265686075>

Additional Information

Place of birth: Allentown, PA, USA

Current Appointments and Leadership Positions

Faculty Appointment

12/2021 Associate Professor (Clinical), Dept of Medicine, NYU Langone Health, NY
03/2018 Member, Perlmutter Comprehensive Cancer Center, New York, NY

Hospital Appointment

03/2018 Attending Physician, NYU Langone Health, NY

Administrative Leadership Positions

03/2024 Service Chief, GI Oncology, Perlmutter Cancer Center, NYU, NY
09/2024 Co-Director, Pancreas Disease Center, NYU Langone Health, NY
03/2018 Leader, GI Disease Management Group, PCC, New York, NY

Education and Training

Education

09/2000		Biophysics	Bar-Ilan University	Israel
06/2002	BS	Biochemistry	University of Maryland	College Park, MD
06/2006	MD	Medicine	Ohio State University	Columbus, OH
05/2015	MS	Biostatistics	Columbia University	New York, NY

Postdoctoral Training

06/2006-06/2009 Resident, Internal Medicine, Temple University Hospital, Philadelphia, PA
06/2010-06/2013 Fellow, Hematology and Oncology, Columbia University, NY, NY
05/2012-06/2014 Clinical Research Fellow, Olive Lab, Columbia University, New York, NY
06/2013-05/2015 Patient Oriented Research Fellowship, Columbia University, New York, NY

Specialty Certification

2009	American Board of Internal Medicine, Internal Medicine
2014	American Board of Internal Medicine, Medical Oncology

Licensure

2010-	New York	#257682
2006-2010	Pennsylvania	

Previous Appointments and Leadership Positions

Faculty Academic Appointments

03/2018-11/2021	Assistant Professor (Clinical), Dept. of Medicine, NYU Langone Health, NY
07/2013-02/2018	Assistant Professor (at CUMC), Dept. of Medicine, Columbia University, NY
06/2017-03/2018	Member, Irving Comprehensive Cancer Center, New York, NY.

Hospital Appointments

07/2013-02/2018	Assistant Attending Physician, NYP Hospital, New York, NY.
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Administrative Leadership Positions

03/2018- 2/2024	Director, GI Oncology, Perlmutter Cancer Center, NYU, NY
03/2018 -8/2024	Assistant/ Interim Director, Pancreatic Cancer Center, PCC, New York, NY
06/2012-06/2013	Chief Fellow in Hematology/Oncology, Columbia University, New York.

Other Professional Positions

N/A

Awards, Honors, and Memberships in Honorary Societies

Internal

06/2003	OSU Medical School, Roessler Fellowship presented for outstanding research project.
05/2006	OSU Medical School, Landacre Society for Medical Student Research.
06/2013	Columbia University, Patient Oriented Research Scholar.

External

06/2013	ASCO Conquer Cancer Foundation, Young Investigator Award
07/2019	NCI, 2019 Cancer Clinical Investigator Team Leadership Award
01/2023	National Pancreas Foundation, Nobility in Science Award

Research Activity

Research Activities

My major research activities include:

1. Building collaborative teams to design and implement novel translational clinical trials in pancreatic, gastric, and other GI cancers by collaborating with scientists and pharmaceutical partners to advance agents into the clinic and conduct correlative research.
2. Developing team-based approaches to improving care delivery and multi-disciplinary collaborative care in GI cancer patients by focusing on rapid, patient oriented access to expert teams and advanced therapeutics including investigational agents.
3. Advancing novel therapies to support patient quality of life and patient outcomes including focus on physical activity, cachexia, diet and novel therapies in GI cancers.

My work in these areas is focused on improving outcomes for patients with these recalcitrant cancers.

Grant History

Grants and Clinical Trials

Ongoing Research Support

Completed Research Support

National Institution of Health- 1P20CA252728-02 Ahn (PI) 9/17/20-8/31/24
 NYU Cancer Health Disparity (CHD) SPORE
 Role- Co Project Lead of Project 2. Multidisciplinary evaluation of tumor microbiome in orodigestive tract cancers.
 3% effort.

Merck Investigator Studies Program Oberstein (PI) 7/1/20- 12/31/2023
 Sponsored Research Project
A phase II study of lenvatinib, a multi-targeted tyrosine kinase inhibitor, combined with pembrolizumab (PD-1 inhibitor) for the treatment of metastatic gastroesophageal cancer patients who have progressed on first or subsequent line therapies
 Role: PI of multi-center trial.
 5% effort. (project transferred from previous PI who left institution).

Pancreatic Cancer Action Network Simeone (PI) 2/1/20-1/31/24
 Precision Promise Clinical Trial Consortium.
 Role- Co-PI of NYU site in multi-institutional clinical trial network for advanced pancreatic cancer.
 5% effort.

National Cancer Institute (NCI)- RN 01327 Neel (PI) 3/1/2019-2/28/2021
 Cancer Center Support Grant P30 supplement- CCITLA (Oberstein)
 Role- PI of supplemental award to Cancer Center Support Grant to develop collaborative clinical trials.
 15% effort.

Pancreatic Cancer Action Network Wang (PI) 7/1/17- 6/30/19
 Translational Research Grant
Targeting cholinergic receptors to suppress pancreatic cancer.
 Total grant: \$300,000.
 Role- Co-PI and lead of clinical component. 10% effort.

UG1 CA189960-01 Schwartz (PI) 2017-2018
 Supplemental Contract Award- Parent NCORP Grant UG1 CA189960-01
Project Title: Columbia University Minority/Underserved Site NCI Community Oncology Research Program, NCI PDX Study Tissue Supplement.

In this project, I will coordinate collection of tissue and blood samples from 30 newly diagnosed rare cancer patients for development of models in the NCI PDX program.

Direct Funding: \$90,000 year based on accrual, renewable for 1 additional year.

Role: Project PI. 10% effort.

Merck Investigator Studies Program Oberstein (PI) 1/1/17-2/28/18
Sponsored Research Project
Phase II study of chemotherapy and immune checkpoint blockade with Pembrolizumab in the perioperative and maintenance treatment of locoregional gastric or GE junction adenocarcinoma.
Total Contract: \$987,544.00.
Role: PI of multi-center trial. 10% effort.

Irving Institute for Clinical and Translational Research Han (PI) 3/1/17-2/28/18
Precision Medicine Pilot Award
Precision T cell receptor based therapies in cancer treatment.
Role: Collaborator. Led development of the clinical protocol and IRB submission and patient recruitment.

Merck Investigator Studies Program Oberstein (PI) 8/1/17-2/28/18
Sponsored Research Project
Phase II open-label, single-center study evaluating safety and efficacy of pembrolizumab following induction with the hypomethylating agent Azacitidine in patients with advanced pancreatic cancer after failure of first-line therapy.
Total Contract: \$987,537.30.
Role: PI. 10% effort.

KL2 TR000081 Ginsberg (PI) 7/1/15-6/30/17
Clinical and Translational Science Award
Developing Validated Models to Measure Tumor Associated Cachexia in Pancreatic Cancer
The goal of this mentored research study is to assess the correlation between various imaging and pathological measurements to measure tumor associated cachexia.
Direct Cost: \$75,000.
Role: PI of mentored project. 50% effort.

UG1 CA189960-01 Schwartz (PI) 2015-2016
Supplemental Award- Parent NCORP Grant UG1 CA189960-01
Project Title: Columbia University Minority/Underserved Site NCI Community Oncology Research Program, NCI PDX Study Supplement.
In this project, I coordinated collection of blood samples from 100 newly diagnosed advanced cancer patients for support of the NCI PDX program.
Total Cost: \$100,000.
Role: Project PI. 10% effort.

Young Investigator Award (YIA) Oberstein (PI) July 2013- June 2014
American Society of Clinical Oncology
Evaluation of the therapeutic effect of a small molecule inhibitor of the oncoprotein BMI1 in pancreatic cancer.
Mentor: Kenneth Olive, PhD
Sponsor: Alfred I. Neugut, MD, PhD
Total Cost: \$50,000.
Role: PI, 50% effort.

Active Clinical Trials

Study of RMC-9805 in Participants With KRAS G12D-Mutant Solid Tumors. 2024-

Sponsor: Revolution Medicines, Inc. NCT06040541

Role: **Site Principal Investigator**

A Study of LY3962673 in Participants With KRAS G12D-Mutant Solid Tumors. 2024-

Sponsor: Eli Lilly. NCT06586515

Role: **Site Principal Investigator**

A Phase IB Study to Determine the Safety and Tolerability of Canakinumab and Tislelizumab in Combination With Nab-Paclitaxel and Gemcitabine in the Neo-adjuvant Treatment of Patients With Pancreatic Cancer. 2023-

Sponsor: NYU. NCT05984602

Role: **Principal Investigator, Investigator Initiated, IND Holder**

Feasibility of a Health Care Provider Guided Exercise Intervention Prior to Surgical Resection of Pancreatic Cancer. 2022- 2025

Sponsor: NYU. NCT05483075

Role: **Principal Investigator, Investigator Initiated**

A Study to Evaluate ATP150/ATP152, VSV-GP154 and Ezabenlimab in Patients With KRAS G12D/G12V Mutated PDAC (KISIMA-02). 2023-

Sponsor: AMAL Therapeutics. NCT05846516

Role: **Global Coordinating Principal Investigator**

Randomized Phase II/III Trial of 2nd Line Nivolumab + Paclitaxel + Ramucirumab versus Paclitaxel + Ramucirumab in Patients with PD-L1 CPS $\geq$ 1 Advanced Gastric and Esophageal Adenocarcinoma (PARAMUNE), SWOG S2303. 2023-

Sponsor: SWOG (NCTN). NCT06203600

Role: **National Co-Chair, Site co-Investigator**

RASolute 302: A Phase 3 Multicenter, Open-label, Randomized Study of RMC-6236 versus Investigator's Choice of Standard of Care Therapy in Patients with Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC). 2024-

Sponsor: Revolution Medicine Inc. NCT06625320

Role: **Site Principal Investigator**

Testing the Addition of Pembrolizumab, an Immunotherapy Cancer Drug to Olaparib Alone as Therapy for Patients With Pancreatic Cancer That Has Spread With Inherited BRCA Mutations. 2024-

Sponsor: ECOG (NCTN). NCT04548752

Role: **Site Principal Investigator**

APOLLO: A Randomized Phase II Double-Blind Study of Olaparib Versus Placebo Following Curative Intent Therapy in Patients With Resected Pancreatic Cancer and a Pathogenic BRCA1, BRCA2 or PALB2 Mutation. 2022-

Sponsor: ECOG (NCTN). NCT04858334

Role: **Site Principal Investigator**

A Phase 1b/2, Open-Label Study of Amivantamab Monotherapy and in Addition to Standard-of-Care Chemotherapy in Participants with Advanced or Metastatic Colorectal Cancer. 2022-2024.

Sponsor: Janssen Therapeutics. NCT05379595

Role: Site Principal Investigator

A022104 The Janus Rectal Cancer Trial: A Randomized Phase II Trial Testing the Efficacy of Triplet Versus Doublet Chemotherapy to Achieve Clinical Complete Response in Patients with Locally Advanced Rectal Cancer. 2024-

Sponsor: Alliance (NCTN). NCT05610163

Role: **Site Co-Investigator**

A Phase 1/2 Study to Evaluate the Safety and Efficacy of MK-2870 Monotherapy or in Combination With Other Anticancer Agents in Gastrointestinal Cancers. 2024-

Sponsor: Merck. NCT06428409

Role: **Site Principal Investigator**

A Phase I/IIa Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AZD0022 as Monotherapy and in Combination with Anti-cancer Agents in Adult Participants with Tumours Harboring a KRASG12D Mutation. 2024-

Sponsor: Astra Zeneca. NCT06599502

Role: **Site Co-Investigator**

A phase II study (with safety run-in) of ALX148 in combination with cetuximab and pembrolizumab in patients with refractory microsatellite stable metastatic colorectal cancer. 2023-

Sponsor: AGICC. NCT05167409

Role: **Site Co-Investigator**

A Randomized Open-Label Phase 3 Study of XL09 + Atezolizumab vs Regorafenib in Subjects with Metastatic Colorectal Cancer (STELLAR). 2023-2024.

Sponsor: Exelixis. NCT05425940

Role: **Site Principal Investigator**

A Randomized Phase 3 Study of MRTX849 in Combination with Cetuximab Versus Chemotherapy in Patients with Advanced Colorectal Cancer with KRAS G12C Mutation with Disease Progression On or After Standard First-Line Therapy. 2021-

Sponsor: Mirati. NCT04793958

Role: **Site Principal Investigator**

Phase II pilot study of FOLFOXIRI plus panitumumab in metastatic RAS wild-type, left-sided colorectal cancer. 2020- 2024

Sponsor: AGICC. NCT04169347

Role: **Site Co-Investigator**

Phase 1b Study to Evaluate ATP128, VSV-GP128 and BI 754091, in Patients With Stage IV Colorectal Cancer (KISIMA-01). 2022-2024.

Sponsor: Amal Therapeutics. NCT04046445

Role: **Site Principal Investigator**

BASECAMP-1: An Observational Study Obtaining Solid Tumor Tissue From Subjects With Primary Surgical Resection and Leukapheresis for CAR T-Cell Therapy Manufacturing, 2021-

Sponsor: A2 Therapeutics Inc. NCT04981119

Role: Site Co-Investigator

Orodigestive (ODT) Cancer Multi-Ethnic Cohort. 2020-

Sponsor: NYU (NCI).

Role: **Principal Investigator**

Completed Clinical Trials (partial list)

A Phase II a Study of Lenvatinib, a Multi-targeted Tyrosine Kinase Inhibitor, Combined With Pembrolizumab (PD-1 Inhibitor) for the Treatment of Metastatic Gastroesophageal Cancer Patients Who Have Progressed on First or Subsequent Line Therapies. 2018-2023.

Sponsors: Eisai and Merck. NCT03321630

Role: **Principal Investigator, Investigator Initiated, IND Holder**

A Phase 3, randomized, double-blind study of pamrevlumab or placebo in combination with gemcitabine plus nab-paclitaxel as neoadjuvant treatment in patients with locally advanced, unresectable pancreatic cancer. 2020-2023.

Sponsor: Fibrogen. NCT03941093

Role: **Site Principal Investigator**

A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT). 2020-2022.

Sponsor: Corcept. NCT04329949

Role: **Site Principal Investigator**

A Multicenter, Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumor (LEAP-005). 2019-2021.

Sponsor: Merck.

Role: **Site Principal Investigator**

A Phase 2 Study of APX005M in Combination with Concurrent Chemo-radiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers. 2021-2023.

Sponsor: Apexigen. NCT03165994

Role: **Site Principal Investigator**

A Phase 1b Study to Determine the Safety and Tolerability and Confirm the Dose of Canakinumab and Spartalizumab in Combination With Nab-paclitaxel and Gemcitabine for Patients with Metastatic Pancreatic Cancer. 2020-2023.

Sponsor: PANCAN and Novartis. NCT

Role: **Principal Investigator, Investigator Initiated**

A Randomized Phase 2 Study of Losartan and Nivolumab in Combination with FOLFIRINOX and SBRT in Localized Pancreatic Cancer. 2018-2022.

Sponsors: Stand Up to Cancer, BMS.

Role: **Site Principal Investigator**

A Phase 1 Study to Evaluate the Safety and Tolerability of AB680 Combination Therapy in Participants with Gastrointestinal Malignancies. 2020-2022.

Sponsor: Arcus Biosciences.

Role: **Site Principal Investigator**

A Phase 1 b/2, Open-Label, Randomized Platform Study Evaluating the Efficacy and Safety of AB928-Based Treatment Combinations in Patients with Metastatic Colorectal Cancer. 2021-2023.

Sponsor: Arcus Biosciences.

Role: **Site Principal Investigator**

A randomized, double-blind, phase III study comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC). 2021-2023.

Sponsor: Novartis.

Role: **Site Principal Investigator**

A Phase 1b/2 Randomized Study of AVB-S6-500 Plus Nab-paclitaxel and Gemcitabine in Patients With Locally Advanced or Metastatic Pancreatic Adenocarcinoma. 2021-2023.

Sponsor: Aravive.

Role: **Site Principal Investigator**

A Phase 2 Study of Cabiralizumab (BMS-986227, FPA008) Administered in Combination with Nivolumab (BMS-936558) with and without Chemotherapy in Patients with Advanced Pancreatic Cancer. 2018-2020.

Sponsor: BMS. NCT

Role: **Site Principal Investigator**

Clinical Activity

I lead the GI Oncology practice within the Perlmutter Cancer Center at NYU Langone Health. I have primary oversight of 10 physicians and patient care teams in Manhattan, Brooklyn, and Long Island. Our group sees over 1500 new unique GI Cancer patients per year and has over 350 encounters a week. I oversee weekly meetings with multidisciplinary teams including medical oncology, radiation oncology, palliative care, social work, nutrition, and research to provide group oversight and expert care. I devote 50% of my effort in the outpatient clinic focusing on GI malignancies with emphasis on pancreatic, gastric and colon cancers and 2 weeks per year on the inpatient Oncology service. Since coming to NYU in 2018, I have instituted rapid access referrals in our clinics, leading to increased multidisciplinary collaboration, increased clinical trial participation and increased volumes by over 100%.

Education Activity

My educational activities are focused on training medical oncology fellows and Internal Medicine residents in oncology care and clinical research. In addition to mentoring in my clinics, I have aggressively increased didactic lectures in GI cancers and engaged trainees broadly in exploring clinical questions in GI Oncology. I have mentored multiple trainees and collaborated with several basic science partners to help lab trainees gain clinical and translational exposure and develop new projects.

Teaching Activities (see description)

2020- 2022	4 Part Lecture Series- Introduction to Clinical Research for Hematology/ Oncology fellows. Lecture series introducing regulatory and statistical principles of clinical and translational research for fellows. 40 hours in year 1.
2020- 2025	Fellowship Didactics Teaching in fellowship program, 3-4 lectures per year to Medical Oncology and Radiation Oncology trainees in GI Cancers.
2021- 2025	Translating Cancer Discovery into Clinical Practice, BMSC-GA 4422

Graduate level seminar in translational cancer research and application.
Annual seminar in GI Cancer translational research.

12/2018- 2025	Teaching in medical school curriculum, Oncology Small Group Session Leader, medical students, 4 hours per year.
7/2013- 11/2017	Teaching to various fellows, Columbia University Medical Center including medical oncology fellows (3 hours/year), GI fellows (2 hours), palliative care fellows (2 hours), 12 hours per year.
08/2014- 07/2017	Teaching in medical school curriculum, course lecturer (Pancreatic Cancer) and group discussion leader, The Body in Health and Disease, Pathophysiology of Oncology, Columbia University Medical School, 6 hours per year.
09/2017- 05/2017	Teaching in medical school curriculum, Clerkship Supervisor, Foundation of Clinical Medicine 1 Clerkship, Columbia University. 6 hours per year.

Curriculum development and other innovative educational activities

01/2020	Received NCI funded award to design and implement an introductory 4 part lecture series on clinical and translational research. Designed lectures covering trial design, basic biostatistics in collaboration with additional faculty, regulatory considerations, and practical applications. 40 hours in first year.
10/2019	Developed new didactic course for fellowship program, recruited 9 faculty members to participate, designed the curriculum and led lectures to provide a comprehensive course in all aspects of GI cancers including pathology, genetics, and translational research. 20 hours in first year.

Invited Talks and Teaching of Peers

Internal

Sponsored by NYU Langone Health

03/2018- current	Lead or co-lead multidisciplinary educational tumor boards at NYU Langone Health. These include primary oversight for weekly GI Oncology tumor board with over 40 participants from all campuses; leadership of monthly Neuroendocrine Oncology Tumor Board, leadership role in weekly Pancreatic Cancer tumor board, and participation in weekly Multidisciplinary Liver Radiology Conference.
11/13/2024	Sports Health Grand Rounds, Exercise is Medicine, NYU Langone Health. "Cancer and Exercise"
May 2023	Pancreatic Cancer Center Research Seminar Series. "Clinical Trials in Pancreatic Cancer- Updates and Opportunities"
1/23/24	GI Grand Rounds, Division of Gastroenterology, NYU Langone. "Novel Treatment Paradigms in GI Cancers- 2023"

11/6/2018 Oncology Grand Rounds, NYU Winthrop, “Multidisciplinary Approached to Localized Disease in Pancreatic Cancer”

10/30/2018 GI Grand Rounds, Division of Gastroenterology, “Progress in Pancreatic Cancer”

Sponsored by all other NYU schools

1/10/2025 NYU Langone Health Big Gut Seminar Series in Pancreatic Diseases. “Adoptive Cell Therapy in Pancreatic Cancer: CAR-T, TILs and Beyond”

March 2024 NYU Langone Health, Community Webinar on **Colorectal Cancer: Prevention, Screening & Treatment**. “Advancements in Treatment Options in Colon Cancer”

5/5/2023 NYU Langone Health Big Gut Seminar Series in Pancreatic Diseases. “Novel Clinical Trials in Pancreatic Cancer”

Feb 2020- Invited lecture, Colorectal Cancer Immunology, BIOL-GA 1011, Spring 2020 Advanced Immunology, Gastrointestinal Immunology Course. Course Director: Carol Shoshkes Reiss, PhD.

[External to NYU Langone Health and all other NYU schools](#)

September 2025 “Toxicity management for KRAS-targeted therapy in GI Tumors”; “Identifying and treating MTAP deficiency in GI tumors”; “Amivantamab plus FOLFOX or FOLFIRI in metastatic CRC”. **Invited lectures at DAVA Oncology 2025 Bermuda GI Summit.**

11/14/2024 “Exploring Combination Therapies Utilizing KRAS G12D Inhibitors in Pancreas Cancer” **Inaugural New York Pancreatic Cancer Consortium.**

September 2024 “Mechanisms of Resistance to KRAS Inhibition in Pancreas Cancer”. “IL-1b Targeted Therapy in PDAC: Biological Correlates and Neoadjuvant Therapy”. “Amivantamab, an EGFR/C-MET Bispecific in Colorectal Cancer.” “RMC-9805, A KRAS G12D Inhibitor for KRAS G12D-Mutated Solid Tumors”. **Invited lectures at DAVA Oncology 2024 Bermuda GI Summit.**

May 2023 “Novel Clinical Trials in Pancreatic Cancer.” **Invited lecture at Taipei Veterans General Hospital, Taipei City, Taiwan.**

Feb 2022 “Colorectal Cancer- Updates and Novel Agents” **OncLive Institutional Perspectives in Cancer Series, New York.**

May 2018 “Incorporating Novel Agents and Sequencing Approaches in Advanced Pancreatic Neoplasms.” **OncLive State of the Science Summit, New York.**

Jan 2015 Visiting Professor Lecture, “Pancreatic Cancer in 2015”. Department of Radiology, **University of Vermont Medical Center.**

March 2015 Cancer Center Grand Rounds. “Pancreatic Cancer; Progress and Challenges.” Norris Cotton Cancer Center, **Dartmouth-Hitchcock Medical Center.**

Feb 2013 Oncology Seminar Series. “Epithelial Stromal Interactions in a Mouse Model of Pancreatic Cancer.” **Weill Cornell Medical Center, NY.**

June 2013 Hematology/Oncology Grand Rounds Seminar. “Paradoxical Acceleration of Pancreatic Cancer Due to Hedgehog Inhibition.” Department of Medicine, **Columbia University Medical Center.**

Mentoring and Advising

Predoctoral students supervised and/or mentored

2019- 2023 Emma Kurz, NYU Langone MD/PhD program, Advisor on thesis committee and translational mentor for clinical trial development.
Current Position: Internal Medicine Resident, Mass General Hospital

Postdoctoral students supervised and/or mentored

07/2024- Alessandro Leal, NYU Hematology/Oncology program, clinical and translational research mentor.
Mentee was awarded a Young Investigator Award from ASCO (2025)
Current Position: Senior Fellow at NYU Langone Health

07/2020- Peter Yu, NYU Hematology/Oncology program, clinical and translational research mentor.
Mentee was awarded a Young Investigator Award from ASCO (2022) and KL2 Career Development Award (2024).
Current Position: Instructor, NYU Langone Health

07/2019- 2023 Chengwei Peng, NYU Hematology/Oncology program, clinical and translational research mentor.
Mentee was awarded a Young Investigator Award from ASCO (2022).
Current Position: Assistant Professor, Feinberg School of Medicine, Chicago, IL.

07/2018- 2021 Benjamin Krantz, NYU Hematology/Oncology program. Clinical mentor.
Current Position: Clinical Assistant Professor, NYU Langone Health. Biotech executive.

09/2018- 2021 Ajay Prakash, NYU Hematology/Oncology program. Clinical research mentor.
Current Position: Assistant Professor, University of Minnesota Medical School

08/2016- 2018 Ruth White, Columbia University. Clinical mentor, Instructor- Columbia University.
Mentee was awarded a Young Investigator Award from ASCO (2018).
Current Position: Assistant Professor, NYU Langone Health, New York.

07/2016- 2018 Rachael Safyan, Columbia University. Clinical and Research mentor, Assistant Professor- Columbia University.
Mentee was awarded a Young Investigator Award from ASCO (2017).
Current Position: Assistant Professor, University of Washington, Fred Hutch Cancer Center, Seattle WA.

Faculty mentored

07/2018- 2022 Despina Siolas, NYU Division of Hematology/Medical Oncology.
Clinical mentor and faculty advisor on K08 (CA241341).
Current Position: Assistant Professor, Cornell University, New York.

Institutional, Local/National Service and Related Activity

Institutional Service

- 2014- 2018 Member, Protocol Review and Monitoring Committee, Herbert Irving Comprehensive Cancer Center.
- 2015- 2018 Member, Clinical Competency Committee, Division of Hematology/Oncology, Columbia University.
- 2008-2009 Member, Pharmacy and Therapeutics Committee, Temple University Hospital.

Professional Service

Professional Service for Professional Organizations

- 2010- Member, American Society of Clinical Oncology
- 2012- Member, American Association of Cancer Research
- 2013- Member, Southwest Oncology Group Network.
- 2013- Member, Gastrointestinal Committee, Southwest Oncology Group.
- 2018- Member, Clinical Trial Consortium Committee, Precision Promise, Pancreatic Cancer Action Network.
- 2018- Member, Supportive Care Committee, Precision Promise, Pancreatic Cancer Action
- 2019-2020 Member, Arm Selection Committee, Precision Promise.

Peer Review Groups, Grant Application Review Groups, and Study Sections

- 2013- 2015 PCORI Institute, Washington, DC- Stakeholder Reviewer
- 2015- 2018 Irving Institute of Clinical and Translational Research- Collaborative and Multidisciplinary Pilot Research Grants- Scientific Reviewer.
- 2015- 2018 Irving Institute of Clinical and Translational Research Clinical Trials Pilot Award- Scientific Reviewer.

Advisory Boards and Consultant Positions

- 2023- GI Steering Council Member- AstraZeneca Partners in Care Network
- 2017- 2023 US Gastric Advisory Board- Merck
- 2018- 2021 Scientific Advisory Board- Tyme Inc.
- 2019- 2021 Ad Hoc Member, National Steering Committee, PANC003 Trial (NCT03504423).
- 2020- 2022 Scientific Advisory Board- Rubius Therapeutics
- 2024- Scientific Council- Ipsen Biopharmaceuticals
- 2023- Steering Committee and Global PI- Amal Therapeutics

Organizing Roles in Scientific Meetings

- 2013-2017 Co-Organizer, Gig Shaw Symposium on Pancreatic Disease at the Pancreas Center of Columbia University. With a co-organizer, led all aspects of planning for a highly

successful biennial conference of external and internal speakers in pancreatic cancer (2013, 2015, 2017)

Editorial and Journal Positions

Ad Hoc JAMA, Journal of Clinical Oncology, Therapeutic Advances in Gastroenterology, Gastroenterology, JNCCN, Oncologist, Cancer Discovery, Clinical Cancer Research.

Community Service, Volunteer Activities, and Teaching of Patients

2016- Volunteer, Lustgarten Foundation.

2019- Volunteer and Advocate, Pancreatic Cancer Action Network

Military Service

N/A

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Peer-reviewed Publications

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Patents

N/A

APPENDIX B

Reference Name and Year Published	Regimen Administered	Modifications From Standard FOLFIRINOX	Treatment Administered In First- / Second-Line Patients	Conclusion
Prospective Studies				
Vasile 2012	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,800 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan 400 mg increased 5-FU(iv) Removed 5-FU(bolus)	No prior treatment information	“Chemotherapy with mFOLFOXIRI seems active in locally advanced pancreatic cancer patients and may allow to obtain a downstaging of disease leading some patient to achieve a curative surgical resection.”
James 2014	Oxaliplatin: 85 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 300 mg/m2	25% reduced irinotecan 25% reduced 5-FU(bolus)	First-line	“mFOLFIRINOX, given along with prophylactic pegfilgrastim is associated with a similar RR and improved tolerability compared to full dose FOLFIRINOX in advanced PC.”
Stein 2016	Oxaliplatin: 85 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 300 mg/m2	25% reduced irinotecan 25% reduced 5-FU(bolus)	First-line	“In this first prospective study of modified FOLFIRINOX in MPC and LAPC, we observed decreased AEs compared with historical control patients. In MPC, the efficacy appears comparable with FOLFIRINOX.”
Yoshida 2017	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	“Compared to FX, mFX may result in fewer Grade 3 or 4 nonhematological AEs, with a comparable response rate. However, further efforts might be required to reduce hematological AEs.”
Li 2017	Oxaliplatin: 68 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	20% reduced oxaliplatin 25% reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	“In summary, we showed that our modified-FOLFIRINOX was well tolerated in MPC patients, with an ORR of 32.5%, median OS of 10.3 month, and PFS of 7.0 months. . . . To our knowledge, this is the first prospective study aiming to evaluate the efficacy of FOLFIRINOX in Chinese MPC patients, and they did benefit from dose reduction with improved safety and similar tumor response.”
Ozaka 2018	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	“In conclusion, this is the first prospective study of modified FOLFIRINOX in Asia. The modified FOLFIRINOX regimen in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim.”

Wang 2019	Oxaliplatin: 65 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	20 mg reduced oxaliplatin 30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	“The efficacy of this modified FOLFIRINOX was comparable to that of the original regimen but with a notably lower rate of adverse events.”
Ramanathan 2019	Oxaliplatin: 85 mg/m2 Irinotecan: 180 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	Removed 5-FU(bolus) Added PEGPH20 (recombinant hyaluronidase)	First line	“The control arm of mFOLFIRINOX was remarkably well tolerated and resulted in a median OS of 14.4 months, which is—to our knowledge—the highest reported for this regimen.”
Wei 2019	Oxaliplatin: 72.25 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	15% reduced oxaliplatin 25% reduced irinotecan Removed 5-FU(bolus)	First-line	“[W]e provide evidence that pretreatment ctDNA level correlates with tumor burden in PDAC, and serial cfDNA analysis is a robust tool for monitoring cancer response to chemotherapy.”
Vivaldi 2021	Oxaliplatin: 85 mg/m2 Irinotecan: 165 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 3,200 mg/m2 5-FU(bolus): 0 mg/m2	15 mg reduced irinotecan 800 mg increased 5-FU(iv) Removed 5-FU(bolus)	First-line	“For patients with at least one mutated allele of UGT1A1, careful management of hematological and gastrointestinal toxicity is recommended, and a modified FOLFIRINOX with a dose reduction of 30% of irinotecan in homozygous patients might be appropriate.”
Retrospective Studies				
Gunturu 2012	Variable	Median Relative Dose Intensity Compared to FOLFIRINOX: Oxaliplatin: 90% Irinotecan: 64% Leucovorin: undisclosed 5-FU(iv): 100% 5-FU(bolus): 66%	First-line and second-line patients	“In this single institution retrospective study, the routine use of modest dose attenuations of FOLFIRINOX, in conjunction with growth factor support, was associated with improved tolerability compared to full dose FOLFIRINOX as reported by Conroy et al. Our findings suggest that these modest dose attenuations do not reduce the efficacy of FOLFIRINOX in metastatic pancreatic cancer patients. Moreover, the efficacy of FOLFIRINOX in locally advanced disease was comparable to its efficacy in metastatic disease.”
Peddi 2012	Variable	Median Dose Intensities for First Cycle for Each Component: 100% Average Dose Intensities for First Cycle:	First-line and second-line patients	“In spite of dose reductions, FOLFIRINOX was found to be very effective. Rates of response were similar to the ACCORD study with more than 70% of patients having at least stable disease on therapy. Similar response rates were seen in non-metastatic patients who were not included in the ACCORD trial. In fact, 8

		Oxaliplatin: 98% Irinotecan: 90% Leucovorin: undisclosed 5-FU(iv): 99% 5-FU(bolus): 59% Overall Average Dose Intensities: Oxaliplatin: 96% Irinotecan: 88% Leucovorin: undisclosed 5-FU(iv): 96% 5-FU(bolus): 57%		patients were able to undergo resection after FOLFIRINOX therapy. This is notable given the extensive desmoplastic stroma reaction in localized disease and concern for reduced efficacy of chemotherapy in this setting. Progression-free and overall survivals were longer than the results published in the ACCORD trial (7.5 months and 13.5 months, respectively) likely reflecting inclusion of patients with non-metastatic disease. One-year survival rate for patients with metastatic disease was 41.8%, similar to the 48.4% reported in the ACCORD trial.”
Lowrey 2012	Variable	Median Starting Dose 80% of that used in PRODIGE/ACCORD trial	First-line	“We observed activity and acceptable toxicity in carefully selected patients treated with FFX at 80% dose intensity and routine use of growth factor support. Treatment with FFX resulted in median OS of > 1 year in pts with stage IV PAC and is an active front-line regimen.”
Hosein 2012	Variable	Dose Intensity Oxaliplatin: 98% Irinotecan: 95% Leucovorin: undisclosed “5-fluorouracil”: 98%	First-line	“Neoadjuvant therapy with FOLFIRINOX in patients with unresectable or borderline resectable locally advanced pancreatic cancer appears to be feasible in selected patients.”
Alessandretti 2013	Variable	Median Reductions in Dose Compared to FOLFIRINOX: <u>First Cycle:</u> Oxaliplatin: 23.3% Irinotecan: 24.6% Leucovorin: undisclosed “Fluorouracil”: 20.6% <u>Fourth Cycle:</u> Oxaliplatin: 20.8% Irinotecan: 24.9% Leucovorin: undisclosed “Fluorouracil”: 17.6%	No prior treatment information	“Modified dose-attenuated FOLFIRINOX is a therapeutic option to elderly with advanced pancreatic adenocarcinoma. Although grade 3 and 4 toxicities were reported, they were manageable.”

Mahaseth 2013 (Ex. 1005)	Oxaliplatin: 85 mg/m ² Irinotecan: 180 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	Removed 5-FU(bolus)	No prior treatment information	“Overall our modified regimen was well tolerated. . . . The modified FOLFIRINOX regimen appears to have an improved safety profile especially with respect to neutropenia, fatigue, and vomiting.”
Blazer 2014	Oxaliplatin: 85 mg/m ² Irinotecan: 165 mg/m ² Leucovorin: 0 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	15 mg reduced irinotecan Removed leucovorin Removed 5-FU(bolus)	No prior treatment information	“Neoadjuvant mFOLFIRINOX is an effective, well-tolerated regimen for patients with advanced nonmetastatic pancreatic cancer. When mFOLFIRINOX is coupled with aggressive surgery, high resection rates are possible even when the initial imaging shows locally advanced disease.”
Ghorani 2015	Oxaliplatin: 85 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	25% reduced irinotecan Removed 5-FU(bolus)	No prior treatment history information	“Compared to full-dose FOLFIRINOX, our modified regimen resulted in lower haematological but only marginally improved non-haematological toxicity rates, with comparable efficacy outcomes. Prospective studies are required to validate these findings.”
Kaga 2016	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	“We therefore clinically utilized irinotecan dosage of 150 mg/m ² for patients enrolled in this study. The survival time (median PFS, 5.3 months; median OS, 10.3 months) in our cohort was similar to that of the Japanese phase II trial of FOLFIRINOX (median PFS, 5.6 months; median OS 10.7 months) as well as the FOLFIRINOX phase III trial (median PFS, 6.4 months; median OS, 11.1 months).”
de Jesus 2018	Oxaliplatin: 50-85 mg/m ² Irinotecan: 60-180 mg/m ² Leucovorin: 0-400 mg/m ² 5-FU(iv): 1,800-2,400 mg/m ² 5-FU(bolus): 0-400 mg/m ²	Variably reduced all components	First-line	“To conclude, modified FOLFIRINOX demonstrated similar activity to that of standard FOLFIRINOX in patients with MPA. No major differences in toxicity were observed, mainly due to selection bias, uneven dose reductions and unrestricted use of prophylactic G-CSF.”
Kang 2018	Oxaliplatin: 63.75 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 150 mg/m ² 5-FU(iv): 1,800 mg/m ² 5-FU(bolus): 300 mg/m ²	25% reduced oxaliplatin 25% reduced irinotecan 25% reduced leucovorin 25% reduced 5-FU(bolus) 25% reduced 5-FU(iv)	First-line	“mFOLFIRINOX showed comparable efficacy but better safety compared to sFOLFIRINOX. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy.”
Yamada 2018	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	“Modification of the FOLFIRINOX regimen (oxaliplatin 85 mg/m ² , irinotecan 150 mg/m ² , 5-FU infusion 2400 mg/m ² over 46 h, no bolus 5-FU) reduces the incidence of grade 3–4 neutropenia to 47.8%. More importantly, a meta-analysis showed that the modified

				FOLFIRINOX regimen is as effective as the original, with a similar tumor response rate (32% versus 33%, $p = 0.879$), rate of 12-month survival (47% versus 50%, $p = 0.38$), rate of 6-month PFS rate (47% versus 53%, $p = 0.38$) and reduced frequency of grade 3–4 adverse events.”
Eraslan 2019	Oxaliplatin: 65 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 0 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	20 mg reduced oxaliplatin 25% reduced irinotecan Removed leucovorin Removed 5-FU(bolus)	First-line and second-line patients	“In advanced pancreatic cancer patients with good ECOG PS, mFOLFIRINOX treatment provided OS and PFS benefit with manageable toxicity profile. Sustainability of treatment due to side effects is a major problem for both the patient and the physician.”
Sasaki 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	“In conclusion, overall treatment outcomes of chemotherapy for metastatic pancreatic cancer were significantly improved after introduction of FOLFIRINOX and GEM+nab-PTX in the daily practice. However, about 25% of the metastatic pancreatic cancer patients could not be treated with these two effective regimens as first-line chemotherapy. Furthermore, only less than 40% of the patients were treated with these two regimens as second-line chemotherapy. More effective second-line and third-line chemotherapy regimens with less toxicity are required to prolong the overall survival of metastatic pancreatic cancer patients.”
Vivaldi 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 165 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 3,200 mg/m ² 5-FU(bolus): 0 mg/m ²	15 mg reduced irinotecan 800 mg increased 5-FU(iv) Removed 5-FU(bolus)	First-line	“Our results obtained in a large retrospective cohort of metastatic PC patients treated with standard regimens such as modified FOLFIRINOX and GemNab suggest that an earlier and deeper tumor shrinkage is able to predict long-term outcome of PC patients.”
Cavanna 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 320 mg/m ²	25% reduced irinotecan 20% reduced 5-FU(bolus)	First-line	“In conclusion, with the limitations of a retrospective study our results demonstrate that attenuated dose of FOLFIRINOX is feasible in outpatients with metastatic/advanced pancreatic cancer in a general hospital, in the real-world clinical practice, the dose reduction as performed in our patients did not compromise efficacy, but reduced the number of AE.”
Cui 2020	Oxaliplatin: 85 mg/m ² Irinotecan: 140 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ²	40 mg reduced irinotecan	First-line	“In the majority of the patients, the AEs associated with chemotherapy were manageable and tolerable.”

	5-FU(bolus): 400 mg/m2			
Pacheco-Barcia 2020	Oxaliplatin: 85 mg/m2 Irinotecan: 180 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	Removed 5-FU(bolus)	First-line and second-line patients	“In the subgroup analysis defined by treatment, we observed differences between them. The most interesting finding is that when SIRI values were $<2.3 \times 10^9/L$ there were no differences between treatment received; however, in the group of patients with $SIRI \geq 2.3 \times 10^9/L$ we observed a longer OS with mFOLFIRINOX therapy.” “The results of this study suggest that SIRI may be useful in appropriately selecting patients who would benefit of mFOLFIRINOX therapy as a more intensive first-line chemotherapy regimen.”
Takeda 2021	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	“In conclusion, we demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of the novel combination chemotherapy regimens (GnP and mFFX). These two regimens showed a satisfactory radiologic tumor response, PFS, and OS, and was identified as an independent prognostic factor for OS.”
Zhou 2021	Oxaliplatin: 65 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	20 mg reduced oxaliplatin 30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	“In summary, we demonstrated the prognostic value of delta HU for both locally advanced PDAC and advanced PDAC. Delta HU was as a potential marker of predicting chemotherapy response. Patients with higher delta HU will benefit from mFOLFIRINOX treatment. The delta HU was positively correlated with stroma MVD, probably explaining the reason of lower ΔHU associated with worse prognosis.”