

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,

Petitioner,

v.

IPSEN BIOPHARM LTD.,

Patent Owner.

Case No. IPR2025-01531

Patent No. 11,344,552

**EXPERT DECLARATION OF
ROBERT DREICER, M.D., M.S., MACP, FASCO**

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1. I, Robert Dreicer, M.D., M.S., MACP, FASCO, of Earlysville, Virginia, declare as follows:

2. I have been retained by counsel for Petitioner Apotex Inc. (“Apotex”). I understand that Apotex is submitting a petition for inter partes review (“IPR”) of U.S. Patent No. 11,344,552 (“the ’552 patent,” attached as Ex.1001), which is assigned to Ipsen Biopharm Ltd. (“Patent Owner”). It is my understanding that Apotex is requesting that the United States Patent and Trademark Office (“USPTO”) cancel all claims of the ’552 patent as unpatentable. I also understand that CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively “CSPC”) have filed an IPR with respect to the ’552 patent in IPR2025-00505 (the “CSPC IPR”), which the Board has instituted. In support of the CSPC IPR, Mark J. Ratain, M.D. submitted a declaration (Ex.1002). I have reviewed and considered Dr. Ratain’s declaration. I agree with Dr. Ratain’s opinions set forth in his declaration, so I have adopted them. Accordingly, I submit this expert declaration in support of Apotex’s IPR petition for the ’552 patent. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

I. QUALIFICATIONS

3. I graduated from Colorado State University in 1977 with a B.S. degree. I obtained my M.S. from the University of Texas Graduate School of Biomedical Sciences in 1979. I obtained my M.D. from the University of Texas Medical School at Houston in 1983. I completed my internship and residency in internal medicine at Indiana University School of Medicine from 1983-1986. I completed a fellowship in Medical Oncology at the University of Wisconsin Comprehensive Cancer Center from 1986-1988.

4. I am board-certified in Internal Medicine and Medical Oncology. I received my Internal Medicine certification on September 10, 1987 and my Medical Oncology certification on November 7, 1989, with voluntary recertification on May 2, 2013 and am participating in ABIM's maintenance of certification program (LKA).

5. I joined the faculty of the University of Iowa College of Medicine in 1989 as an Associate in the Departments of Internal Medicine and Urology. I was promoted to Assistant Professor in 1990 and to Associate Professor in 1995. From 1999-2001, I served as Associate Division Director of the Division of Hematology/Oncology.

6. From 2001-2014, I served at the Cleveland Clinic in various leadership positions, including Professor of Medicine at the Cleveland Clinic

Lerner College of Medicine (2004-14), Chair of the Department of Solid Tumor Oncology (2006-14), Director of GU Medical Oncology (2000-2014), and Deputy Associate Director for Clinical Research at the Case Comprehensive Cancer Center (2012-2014).

7. Since 2015, I have served at the University of Virginia School of Medicine as Professor of Medicine and Professor of Urology. I currently serve as Head of the Section of Medical Oncology, Deputy Director of the University of Virginia Comprehensive Cancer Center, Associate Director for Clinical Research, and Co-Director of the Paul Mellon Urologic Cancer Institute.

8. I have directed and participated in numerous clinical trials for patients with various malignancies, with particular focus on genitourinary cancers including urothelial (bladder), kidney, and prostate cancers, as well as experience with pancreatic cancer and other solid tumors. I have been directly involved in the design, conduct, and analysis of phase 1, 2, and 3 trials of more than 100 drugs, including small molecule, peptide, and protein drugs. Some of these studies included patients with pancreatic cancer.

9. I have extensive experience in the development of therapeutics for cancer treatment, including combination chemotherapy regimens. This experience includes membership in the Eastern Cooperative Oncology Group (ECOG) Genitourinary Core Committee (1991-2015) and chair of the bladder cancer

subcommittee (1996-2014). I have also served on numerous data safety monitoring boards (Phase I/II and III trials) and scientific protocol review committees.

10. I have also consulted for the pharmaceutical industry for over 30 years, primarily regarding the development and commercialization of oncology drugs. I have interacted extensively with the pharmaceutical industry as an investigator.

11. I have been extensively involved with professional oncology organizations. I have served on the Editorial Board of the Journal of Clinical Oncology (2005-2010), served as a reviewer for numerous journals including the Journal of Clinical Oncology, Cancer, Lancet Oncology, Clinical Cancer Research, European Urology, and Urology, among others. I served 6 years as a member of the American Board of Internal Medicine (ABIM) Oncology Exam Committee and another 6 years as a member of the ABIM Medical Oncology Longitudinal Assessment Approval Committee. I have served as a Deputy Editor for NEJM Journal Watch Hematology/Oncology since 2006.

12. I have served as a research reviewer for multiple committees and working groups at the NIH, including serving as Chair of the Department of Defense Prostate Cancer Research Program Integration Panel (2004-2005) and as a member from 2000-2009.

13. I have received numerous honors and awards throughout my career in recognition of my work in oncology and clinical research. I am a Master of the American College of Physicians (MACP) and a Fellow of the American Society of Clinical Oncology (FASCO).

14. I have been frequently asked to speak at national and international meetings on cancer treatment and drug development. I have given over 250 presentations on various oncology topics, including many on the management of advanced cancers and combination therapies.

15. I have served as an editor and reviewer for numerous journals and have participated in the development of clinical practice guidelines for cancer treatment.

16. I have authored numerous articles in peer-reviewed journals concerning clinical studies and/or pharmacology of cancer drugs. Many of these publications relate to combination chemotherapy regimens and the treatment of advanced cancers.

17. I have experience with pancreatic cancer treatment, including familiarity with the FOLFIRINOX regimen and its modifications. Through my clinical practice and research, I have treated patients with metastatic pancreatic cancer and am familiar with the standard treatment approaches and their evolution over time.

18. I have knowledge and experience with liposomal drug formulations, and understand the rationale for developing liposomal formulations of chemotherapy drugs to modify their pharmacokinetic properties and toxicity profiles.

19. I am familiar with the development of combination chemotherapy regimens and the principles involved in dose optimization to balance efficacy and toxicity. This includes experience with dose modifications based on patient tolerability and toxicity management strategies.

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

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

22. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is normally \$650 per hour, \$5,000 per day for depositions, hearings, etc., that require me to be away from my practice, and \$325 per hour for travel time. My compensation is not dependent in any way upon the outcome of this matter.

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

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

II. SUMMARY OF OPINIONS

25. I have been asked to consider whether claims 1 and 3-15 (“Challenged Claims”) of the '552 Patent are obvious in view of the prior art. The Challenged Claims are directed to methods of treating metastatic pancreatic cancer in a human who has not previously been treated with an anticancer agent with a combination of four chemotherapy drugs: (1) 60 mg/m² of liposomal irinotecan, (2) 60 mg/m² oxaliplatin, (3) 400 mg/m² of leucovorin, and (4) 2400 mg/m² of 5-fluorouracil.

26. In my opinion, claims 1, 3-6, and 8-14 would have been obvious over Conroy, *et al.*, N. Engl. J. Med., 364(19):1817-25 (2011) (“Conroy” (Ex. 1003)) and Mahaseth, *et al.*, Pancreas, 42(8):1311-15 (2013) (“Mahaseth” (Ex. 1005)) in

combination with International Publication No. WO2013/188586A1 (“Bayever” (Ex. 1006)) and the knowledge and skill of a POSA, exemplified by multiple publications regarding liposomal irinotecan, including Saif, *Journal of the Pancreas*, 15(3):278-79 (2014) (“Saif” (Ex. 1007)), Ko, *et al.*, *British J. of Cancer*, 109(4):920-25 (2013) (“Ko” (Ex. 1008)), and Cantore, *et al.*, *Oncology*, 67(2):93-97 (2004) (“Cantore” (Ex. 1009)) and other references discussed herein. My opinions are further supported by post-filing references Nichetti, *et al.*, *JAMA Network Open*, 7(1):1-13 (2024) (“Nichetti” (Ex. 1010)) and Nevala-Plagemann and Garrido-Laguna, *Nature Reviews Clinical Oncology*, 21(8):567-68 (2024) (“Nevala-Plagemann” (Ex. 1011)).

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

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

29. Finally, I am not aware of any secondary considerations that support non-obviousness of the claims. I reserve the right to address any secondary

considerations put forth by Patent Owner (including but not limited to unexpected results) in any later response to this declaration or the petition it accompanies.

III. MATERIALS RELIED UPON

30. I have reviewed the Petition and supporting evidence. I have also reviewed all Challenged Claims of the '552 patent (claims 1 and 3-15), as well as the specification of the '552 patent and relevant parts of its file history, with particular attention to rejections by the Patent Examiner and the responses on behalf of the alleged inventors. I have examined the prior art references asserted against the '552 patent in the Petition. My opinions are based on my own knowledge, experience, and education and with further reference to the exhibits cited herein. I will use the exhibit numbers listed on the "Table of Exhibits" on pages iii-v of the Petition (Paper 1), which I have included for ease of reference below:

LIST OF EXHIBITS

Exhibit	Description
Ex. 1001	U.S. Patent No. 11,344,552 to Bayever <i>et al.</i> ("the '552 patent")
Ex. 1003	Conroy, <i>et al.</i> , N. Engl. J. Med., 364(19):1817-25 (2011) ("Conroy")
Ex. 1004	Certified English Translation of the Protocol of Conroy, et al, https://www.nejm.org , ¹ (2011) ("Conroy Protocol")
Ex. 1005	Mahaseth, <i>et al.</i> , Pancreas, 42(8):1311-15 (2013) ("Mahaseth")
Ex. 1006	International Publication No. WO2013/188586 A1 to Bayever ("Bayever")

¹ <https://www.nejm.org/doi/full/10.1056/NEJMoa1011923#APPNEJMOA1011923PRO>

Exhibit	Description
Ex. 1007	Saif, <i>Journal of the Pancreas</i> , 15(3):278-79 (2014) (“Saif”)
Ex. 1008	Ko, <i>et al.</i> , <i>British J. of Cancer</i> , 109(4):920-25 (2013) (“Ko”)
Ex. 1009	Cantore, <i>et al.</i> , <i>Oncology</i> , 67(2):93-97 (2004) (“Cantore”)
Ex. 1010	Nichetti, <i>et al.</i> , <i>JAMA Network Open</i> , 7(1):1-13 (2024) (“Nichetti”)
Ex. 1011	Nevala-Plagemann and Garrido-Laguna, <i>Nature Reviews Clinical Oncology</i> , 21(8):567-68 (2024) (“Nevala-Plagemann”)
Ex. 1012	Masi, <i>et al.</i> , <i>Annals of Oncology</i> , 15:1766-72 (2004) (“Masi”)
Ex. 1013	Carnevale and Ko, <i>Future Oncology</i> , 12(4):453-464 (2016) (“Carnevale”)
Ex. 1014	Dean, <i>et al.</i> , <i>J Clin Oncol</i> , 34(4 Suppl.):tps482 (2016) (“Dean”)
Ex. 1015	U.S. Provisional Application No. 62/208,209 to Bayever <i>et al.</i> (“the ’209 Provisional”)
Ex. 1016	Ginocchi, <i>et al.</i> , <i>Annals of Oncology</i> , 23(9 Suppl.):ix238 (2012) (“Ginocchi”)
Ex. 1017	Conroy Supplementary Appendix, <i>N. Engl. J. Med.</i> , 364(19): 1817-25 Supplementary Appendix (2011) (“Conroy Appendix”)
Ex. 1018	Wainberg, <i>et al.</i> , <i>Ann Oncol.</i> , 31 (Suppl. 3):S241 (2020) (“Wainberg abstract”), corresponding poster (“Wainberg poster”), corresponding presentation (“Wainberg presentation”)
Ex. 1019	Wainberg, <i>et al.</i> , <i>European Journal of Cancer</i> , 151:14-24 (2021) (“Wainberg 2021”)
Ex. 1020	U.S. Non-Provisional Patent Application No. 15/241,106 to Bayever <i>et al.</i> (“the ’106 Application”)
Ex. 1021	Hatachi, <i>et al.</i> , <i>Cancer Diagn & Progn</i> , 2(1):101-06 (2022)
Ex. 1022	Zaniboni, <i>et al.</i> , <i>Cancer Chemother Pharmacol.</i> , 69(6):1641-45 (2012)
Ex. 1023	Tsai, <i>et al.</i> , <i>J Gastrointest Oncol.</i> , 2(3):185-94 (2011)
Ex. 1024	U.S. Patent No. 8,147,867 to Hong, <i>et al.</i> (“the ’867 patent”)
Ex. 1025	Press Release by Merrimack Pharmaceuticals, Inc. on August 1, 2011
Ex. 1026	International Publication No. WO 2016/094402 A1 to Bayever (“Bayever II”).
Ex. 1027	Alcindor, <i>et al.</i> , <i>Curr Oncol</i> , 18(1):18-25 (2011)
Ex. 1028	U.S. Provisional Application No. 62/216,736 to Bayever <i>et al.</i> (“the ’736 Provisional”)

Exhibit	Description
Ex. 1029	U.S. Provisional Application No. 62/273,244 to Bayever <i>et al.</i> (“the ‘244 Provisional”)
Ex. 1030	U.S. Provisional Application No. 62/281,473 to Bayever <i>et al.</i> (“the ‘473 Provisional”)
Ex. 1031	U.S. Provisional Application No. 62/302,341 to Bayever <i>et al.</i> (“the ‘341 Provisional”)
Ex. 1032	U.S. Provisional Application No. 62/323,245 to Bayever <i>et al.</i> (“the ‘245 Provisional”)
Ex. 1033	Leucovorin Calcium Injection Label (2011)
Ex. 1034	Gemcitabine Injection Label (2012)
Ex. 1035	Abraxane Paclitaxel Label (2013)
Ex. 1036	XELODA Capecitabine Label (2000)
Ex. 1037	Camptosar FDA Label (2006)
Ex. 1038	Eloxatin Oxaliplatin Injection Label (2012)
Ex. 1039	Tarceva Erlotinib Tablets Label (2013)
Ex. 1040	Fluorouracil Injection Label (2012)
Ex. 1041	Conroy, <i>et al.</i> , <i>Curr Oncol Rep.</i> , 15(2):182-9 (2013)
Ex. 1042	Ko, <i>J Clin Oncol</i> , 29(28):3727–29 (2011)
Ex. 1043	Blazer, <i>et al.</i> , ASCO Meeting Abstr. 32(Suppl. 3):275 (2014)
Ex. 1044	Alessandretti, <i>et al.</i> , ASCO Meeting Abstr. 31 (Suppl. 15): e15176 (2013)
Ex. 1045	Paller, <i>et al.</i> , <i>Clin Cancer Res.</i> , 20(16): 4210–17 (2014)
Ex. 1046	Hamberg, <i>et al.</i> , <i>Eur J Cancer</i> , 46(16):2870-78 (2010)
Ex. 1047	Hess, <i>et al.</i> , <i>Annals of Oncology</i> , 21(12):2390-95 (2010)
Ex. 1048	Goel, <i>et al.</i> , <i>Anti-Cancer Drugs</i> , 18(3):263-71 (2007)
Ex. 1049	Rachamalla, <i>et al.</i> , <i>Anticancer Drugs</i> , 15(3):211-7 (2004)
Ex. 1050	Wildiers, <i>Eur J Cancer</i> , 43(15):2235-41 (2007)
Ex. 1051	Gajra, <i>et al.</i> , <i>J Geriatr Oncol</i> , 6(2):133-40 (2015)
Ex. 1052	Shayne, <i>et al.</i> , <i>Cancer</i> , 110(7):1611-20 (2007)
Ex. 1053	Sharma, <i>et al.</i> , <i>J Clinical Oncology</i> , 32(3 Suppl.): 562 (2014)
Ex. 1054	Chang, <i>et al.</i> , <i>Cancer Chemother Pharmacol.</i> , 75(3):579-86 (2015)
Ex. 1055	Roy, <i>et al.</i> , <i>Annals of Oncology</i> , 24(6):1567-73 (2013)
Ex. 1056	Slingerland, <i>et al.</i> , <i>Drug Discov Today</i> , 17(3-4):160-66 (2012)

Exhibit	Description
Ex. 1057	Chen, <i>et al.</i> , <i>J Clin Oncol</i> , 26(15 Suppl.):2565 (2008)
Ex. 1058	Kim, <i>et al.</i> , <i>Cancer Res.</i> , 72(14 Suppl.): A41 (2012)
Ex. 1059	Hann, <i>et al.</i> , <i>Cancer Res.</i> , 67(9 Suppl.): 5648 (2007)
Ex. 1060	U.S. Non-Provisional Patent Application No. 62/343,313 to Bayever et al (“the ’313 Provisional”)
Exs. 1084 – 1123	File History of U.S. Patent No. 11,344,552 Parts 1 to 40

IV. THE UNDERSTANDING APPLIED TO MY ANALYSIS

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

32. I understand that my opinions regarding unpatentability are presented from the viewpoint of a person of ordinary skill in the art (“POSA” or “skilled artisan”) in the field of technology of the patent as of the patent’s priority date. In this declaration, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date for the ’552 patent, which I have been

informed for this proceeding is August 21, 2015. (Ex. 1001 at 2.) To the extent Patent Owner asserts that the claims of the '552 patent are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

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

34. I understand that a limitation can be expressly disclosed by the reference or be inherent. I further understand that for a feature to be inherently disclosed, a POSA would understand the inherent feature would necessarily and inevitably be present when the teaching of the reference is practiced. That is, I

understand that if a feature is not necessarily and inevitably present, it is not inherently disclosed.

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

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

endeavor at the time of invention or addressed by the patent can provide a reason for combining prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

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

38. I understand that a combination of old, familiar, or known elements according to known methods is likely to be obvious when it does no more than yield predictable results. Predictable variations of a work from one field are likely to be obvious, even if the variation is in another field. For example, where a technique has been used to improve a device, use of the same technique to improve

similar devices is a predictable variation and likely obvious. Likewise, if the use of prior art for improvements is simply done according to the prior art's established functions, a POSA has simply implemented a predictable variation. If there existed at the time of invention a known problem for which there was an obvious solution, a patent claim encompassing that solution is not patentable.

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

40. I understand that a claim in a granted patent must be sufficiently supported by the original disclosure of the granted patent, read in the context of what one of ordinary skill in the art would have known at the time of the claimed invention. I understand that the basic inquiry for written description is whether the

specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention.

41. I also understand that claims must be enabled by the original disclosure of the patent. For the claims to be enabled, the information contained in the disclosure must be sufficient to inform those skilled in the relevant art how to make and use the claimed invention without undue experimentation. I understand that the enablement requirement is separate and distinct from the written description requirement.

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

43. Although the following analysis cites to particular pages, lines, paragraphs, or figures of many of the references discussed, these citations are intended to assist in understanding the various bases of my conclusions, and prior art teachings used to reach them. These citations are not intended to be an exhaustive recitation of every page, line number, or paragraph in which these teachings may be found. Similar teachings or disclosures may be found at other

pages, lines, or paragraphs, as well as in other references, and it is to be understood that my opinions and statements are made in view of all of the references and teachings I have reviewed.

V. LEVEL OF ORDINARY SKILL IN THE ART

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

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

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

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

VI. CLAIM CONSTRUCTION

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

49. In my opinion, in view of the specification and prosecution history of the '552 patent, the plain and ordinary meaning of “[a] method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas,” would be understood by a POSA to broadly encompass administration of the recited four-drug regimen for the purpose of alleviating or reducing the symptoms, tumor size, and/or complications associated with metastatic adenocarcinoma of the pancreas or otherwise managing the disease without requiring any specified treatment effect. Specifically, the claims do not require that the treatment regimen be superior to any other standard treatment; simply that the POSA would expect that the treatment regimen be superior to no treatment in some regard. Furthermore, the claims do not require that the treatment

regimen be less toxic than any other treatment; thus, a treatment that is toxic but has a potential therapeutic effect would suffice. The claims also do not require that the treatment regimen has been proven to be superior through a randomized clinical trial or otherwise.

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

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

52. The specification of the '552 patent supports the above construction. For example, in the “Summary” section, the '552 patent states, “Improved antineoplastic therapies for the treatment of pancreatic cancer” and “The improved antineoplastic therapies can provide improved therapeutic index (*e.g.*, improved toxicity profiles) relative to prior FOLFIRINOX regimens.” (Ex. 1001 at 2:23-25.) While the Summary makes this prophetic statement of superiority to a particular prior art regimen, none of the claims make any such statement, and there are no data in the specification that would support the prophecy.

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

54. Similarly, the specification states, “The invention is based in part on the discovery that the administration of a dose of mg/m² liposomal irinotecan was

not well tolerated in humans when administered in combination with” certain drug regimen, and “Accordingly, the preferred methods of treating (previously untreated) pancreatic cancer provide for the administration of a human tolerated antineoplastic therapy.” (*Id.* at 2:57-65; see also *id.* at 2:47-56 (describing other bases for invention).) This again supports the above claim construction that “treatment” does not require actual efficacy, but simply administration of the claimed doses with a therapeutic goal.

55. Additionally, in the “Further Embodiments of Invention,” the specification states, “A method of treating pancreatic cancer | the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.” (*Id.* at 18:32-38.) While the cited sentence uses the phrase “therapeutically effective,” the inventors chose not to include this phrase in any of their claims. In addition, Patent Owner used the word “treatment” synonymously with administration or exposure to. For example, the specification states that “FIG. 6A is a graph showing the percent tumor volume change over time measured in a PDX 190115 pancreatic cancer xenograft mouse efficacy model after **treatment with a saline control...**” (*Id.* at 8:31-36 (emphasis added); see also FIGS. 5A, 5C, 6A-C, and 9 (all showing similar use of the word “treatment”)).

56. The patent applications to which the '815 Application and '552 patent claim priority further support this understanding. For example, in the '209 Provisional, to which the '552 patent claims its earliest priority, the specification defines “effective treatment,” to mean “treatment producing a beneficial effect, *e.g.*, amelioration of at least one symptom of a disease or disorder.” (See Ex. 1015 at ¶ [0036].) The '209 Provisional further states that a beneficial effect can take the form of “an improvement over baseline, *i.e.*, an improvement over a measurement or observation made prior to initiation of therapy” or “arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer.” (*Id.*) The '209 Provisional further states that the term “effective treatment” “may refer to alleviation of at least one symptom of a cancer” or “may, *e.g.*, reduce pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.” (*Id.*) The '209 Provisional also states that the disclosure relates to a “method of treatment (*e.g.*, effective treatment) of metastatic pancreatic cancer in a patient.” (*Id.* at ¶ [0007].) A POSA would understand, especially based on such disclosures in the '209 Provisional, that the term “treatment” simply implied “administration” (with a desire for a beneficial or therapeutic effect) and that “treatment” included both effective treatment and ineffective treatment.

57. The '209 Provisional further defines “effective amount” or “therapeutically effective amount” to mean “an amount of an agent that provides the desired biological therapeutic and/or prophylactic result.” (*Id.* at ¶ [0037].) “That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviating of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.” (*Id.*) Patent Owner clarifies that “[i]n reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation.” (*Id.*) The specification provides examples of an effective amount, which include an amount sufficient to (i) delay tumor development; (ii) prevent or delay tumor recurrence; (iii) reduce the number of cancer cells; (iv) reduce tumor size; (v) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (vi) inhibit (*i.e.*, slow to some extent and may stop) tumor metastasis; (vii) inhibit tumor growth; (viii) prevent or delay occurrence and/or recurrence of tumor; and/or (ix) relieve to some extent one or more of the symptoms associated with the cancer. (*Id.*) A POSA would understand, especially based on such disclosures in the '209 Provisional, that an “effective amount” was one that had been shown to provide one or more of the benefits above.

58. Notably, every provisional application to which the '552 patent claims priority makes this distinction in that they define “effective treatment” and “effective amount” in the same or similar terms as the '209 Provisional and specify that “effective treatment” is just one example of the broader “treatment.” (See Ex. 1028, ¶¶ [0007], [0036]; Ex. 1029, ¶¶ [0007], [0041]; Ex. 1030, ¶¶ [0007], [0047]; Ex. 1031, ¶¶ [0007], [0049]; Ex. 1032, ¶¶ [0007], [0051].) Perhaps more notable, while the term “treatment” is used throughout the '552 patent, the term “effective treatment” is never used the claims (nor are terms like “improved treatment”). (See *generally* Ex. 1001.)

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

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

VII. BACKGROUND AND STATE OF THE ART

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

A. Adenocarcinoma of the Pancreas

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

B. Combination Chemotherapy Was Commonly Used to Treat Pancreatic Cancers

63. Chemotherapy is commonly used for treating pancreatic cancer, either alone or in combination with surgery and/or radiotherapy. For example, by the early 2010s, numerous chemotherapy drugs had been used—alone or in combination—in both first-line and second-line therapies for pancreatic cancer. Of

these, there were seven drugs that were commonly prescribed, which included 5-FU, LV, gemcitabine, nab-paclitaxel, capecitabine, irinotecan, and oxaliplatin. (See, *e.g.*, Ex. 1003 at 2, 7-8; Exs. 1033-1040.)

64. Of the aforementioned agents, only three had received FDA approval for the treatment of pancreatic cancer: 5-FU, gemcitabine, and nab-paclitaxel. (Exs. 1034, 1035, 1040.) While the generic drugs oxaliplatin and irinotecan were never approved for this indication, they were well known to POSAs and widely used and prescribed for pancreatic cancer. (See, *e.g.*, Ex. 1003 at 1-2.) In addition, erlotinib (an oral inhibitor of the epidermal growth factor receptor) had been approved for first-line therapy in combination with gemcitabine but was rarely prescribed for this indication, given its minimal benefit. (Ex. 1039.)

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

65. FOLFIRINOX is comprised of four drugs: oxaliplatin (85 mg/m² over 2 hours), followed by irinotecan (180 mg/m² over 90 min) and LV (400 mg/m² over 2 hours), followed by 5-FU (a 400 mg/m² bolus and 2,400 mg/m² 46 hours continuous infusion). (Ex. 1003 at 1; Ex. 1004 at 5.)

66. Prior to the filing of the '815 Application, Conroy compared FOLFIRINOX with gemcitabine in metastatic PC in a randomized phase 3 trial. (Ex. 1003; see also Ex. 1005.) This study showed significant improvements in, among other things, overall survival (11.1 vs. 6.8 months) with FOLFIRINOX

compared to gemcitabine. (Ex. 1003 at 1; Ex. 1041 at 3.) Based on this study, FOLFIRINOX was considered the most effective regimen for metastatic pancreatic cancer, and it emerged as the new standard of care in appropriate patients with a good performance (*i.e.*, functional) status. (Ex. 1041 at 1.)

67. However, FOLFIRINOX had its drawbacks, including the potential for life-threatening (and even fatal) toxicity, yet with only a small proportion of patients surviving even two years. (Ex. 1003, FIG. 1A; Ex. 1041, Table 1.) For example, FOLFIRINOX was associated with high rates of severe and life-threatening diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory neuropathy. (Ex. 1003 at 8; Ex. 1041 at 3; Ex. 1042 at 1.) Given these toxicities, a POSA was motivated to modify FOLFIRINOX. In fact, modifications to FOLFIRINOX were common. (See, *e.g.*, Ex. 1041, Ex. 1042.)

D. A POSA Understood How To Create Different Combination Regimens

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

a. A POSA Regularly Modified FOLFIRINOX Doses

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

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

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

72. At least for frail and elderly patients, additional adjustments had been made. For instance, in a series of 19 patients over age 65, the bolus of 5-FU was

dropped and doses of both oxaliplatin and irinotecan were lowered (5-FU 2000 mg/m² over 46 h, oxaliplatin 50 mg/m², irinotecan 135 mg/m²). (Ex. 1044 at 1.)

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

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

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

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

76. Likewise, based on a finding that oxaliplatin and irinotecan “have shown cytotoxic synergisms *in vitro* and *in vivo*, with no overlapping toxicity,” Cantore *et al.* published a study of a combination chemotherapy treatment for pancreatic cancer consisting of 60 mg/m² oxaliplatin and 60 mg/m² irinotecan. (Ex. 1009 at 1-5 (finding the treatment an “active and well-tolerated combination in patients with advanced pre-treated pancreatic cancer.”).)

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

77. Dose reduction in chemotherapy is a common and well-established practice across a wide range of cancer types and treatment regimens. Thus, a POSA is highly skilled in reducing chemotherapy doses to mitigate adverse events, either preemptively or after a prior dose based on unacceptable toxicity. A POSA was very familiar with the need to consider lower doses when developing new combinations of known drugs, since the POSA would not expect that all drugs can be administered safely at their standard doses. (See Ex. 1045.) While a POSA would have been motivated to administer the maximal tolerated dose of a combination, a POSA would understand that there were an infinite number of maximal dose combinations. (See Ex. 1046.) As a practical matter, a POSA fixed

the dose of one or more drugs in a combination, and then used routine experimentation to define one or more maximally tolerated dose combinations. (See, *e.g.*, Exs. 1047-49.)

78. Based on the disclosures in the prior art, a POSA would have understood that doses of oxaliplatin in the range of 60-85 mg/m² were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m² FOLFIRINOX dose. A POSA would have used routine experimentation to determine a maximally tolerated combination of 5-FU, LV, oxaliplatin and liposomal irinotecan. (See, *e.g.*, Section VII.D.a-b.) Because most dosing is done in increments of 5 mg/m², a POSA would have a limited number of tolerable doses to choose from and found any oxaliplatin dose within the range of 60-85 mg/m² to be obvious considerations. In addition, a POSA would have been aware of the 60 mg/m² dose of oxaliplatin disclosed in the Conroy protocol for patients who had already experienced toxicity. (See Section VIII.B.) A POSA would have been motivated to select a dose, such as 60 mg/m² that had already been demonstrated to be effective in a similar context (*e.g.*, FOLFIRINOX for pancreatic cancer). (See *id*; see also Section VII.D.b (also disclosing a 60 mg/m² dose of oxaliplatin).)

79. Oncologists often reduce chemotherapy doses preemptively based on clinical judgment, considering factors such as age, treatment intent, comorbidities,

and the toxicity of chemotherapeutic agents, as supported by various studies. (See Ex. 1050; Ex. 1051; Ex. 1052.) A POSA would also be aware that genetics can impact the toxicity of FOLFIRINOX and reduce the irinotecan dose accordingly. (See Ex. 1053 (describing relationship of *UGT1A1**28 allele genotyping to irinotecan toxicity); Ex. 1041 at 4 (stating that “deletion of bolus 5-FU and dose reduction of irinotecan, owing to the presence of the *UGTA1**28/28 genotype, were the commonest modifications”).)

80. Preemptive dose reductions are also common when the treatment intent is palliative rather than curative. Particularly in the setting of incurable metastatic disease, the focus shifts to minimizing toxicity and improving quality of life, which often leads oncologists to favor dose reductions. (Ex. 1050 at 2.) Indeed, a retrospective study found that 25% of 321 patients treated with palliative intent chemotherapy received preemptive dose reductions, compared to 15% of patients who received preemptive dose reductions in the curative setting. (See Ex. 1051 at 1, 4.) Comorbid conditions, such as diabetes, heart disease, and a history of prior cancers, also influence the decision to reduce the dose preemptively. (See *id.* at 4.)

81. Additionally, preemptive dose reductions are commonly observed in patients receiving platinum-containing regimens, such as oxaliplatin. A prospective study of 976 patients treated for common malignancies revealed that significantly

more preemptive dose reductions occurred with platinum-based regimens compared to taxane- and anthracycline-based regimens (41.3% vs. 33.9% vs. 16.4%). (See Ex. 1052 at 4.)

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

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

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

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

85. Onivyde (previously known as MM-398) is one of several liposomal irinotecan formulations that had been evaluated for the treatment of cancer. (Ex.

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

86. An MM-398 liposome is a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. (Ex. 1006 at 9.) MM-398 has a diameter of approximately 80-140 nm and contains distearoylphosphatidylcholine (DSPC), cholesterol (Chol), and N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE) (prepared from poly(ethylene glycol) with molecular weight 2,000) were co-dissolved in chloroform in a molar ratio of 3:2:0.015. (*Id.*; Ex. 1024 at 27:46-51; 91:13-18.) MM-398 can be diluted in

500mL of 5% dextrose injection USP and infused over a 90-minute period. (Ex. 1006 at 9.)

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

88. Patent Owner admits that prior to the filing date of the first provisional application to which the '552 Patent claims priority, liposomal irinotecan (or at least Nal-IRI, aka MM-398) had been studied in multiple clinical trials in patients, including those with metastatic pancreatic cancer. (See Ex. 1015 at ¶ [00203], Table 3 “Summary of Clinical Studies with Nal-IRI.”) The '209 Provisional notes that “[n]ine clinical studies of nal-IRI have been completed to date, with over 400 patients across multiple tumor types exposed to various dosing regimens, with an additional three studies actively recruiting patients across multiple tumor types (see Table 3).” (*Id.* at ¶ [00223] (noting studies were on patients with cervical, gastric, pancreatic, and colorectal cancer, and others).) As exemplified by this disclosure, a POSA at the time would have known that cancer

drugs used to treat one cancer type were often considered as options to treat other cancers.

89. The first clinical results for MM-398 were disclosed in 2008. (Ex. 1057.) Notably, of the 11 patients reported (who received doses of 60-180 mg/m²), one died secondary to diarrhea and neutropenia. Multiple other clinical trials had been completed prior to the filing of the '552 patent application, including one randomized trial in esophageal/gastric cancer, comparing MM-398 to both docetaxel and irinotecan. (See Ex. 1055.)

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

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

when compared with free irinotecan in an orthotopic pancreatic cancer mouse model. (*Id.*; Ex. 1059; Ex 1006 at 25.)

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

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

93. Other known options that were being studied or suggested were modifying known treatments, including those used to treat the same disease (pancreatic cancer) or similar diseases (such as other types of cancer). For example, a POSA would have been aware of FOLFIRINOX because of its

efficacy, but would have also been wary of the toxicities associated with the regimen. As a result, a POSA would have been motivated to modify FOLFIRINOX by reducing the dosages of one or more drugs. (See, *e.g.*, Ex. 1041; supra Section VII.D.) As mentioned above, dosage changes to address toxicity concerns were a regular activity and skill set of a POSA. In addition, a POSA would have been aware of liposomal irinotecan as an alternative to irinotecan. (Supra Section VII.E.) In fact, as further described below, Patent Owner admits that liposomal irinotecan was being studied as a treatment for multiple cancers prior to any application to which the '552 patent claims priority.

A. Conroy (Ex. 1003)

94. Conroy *et al.*, entitled “FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer,” was published in the New England Journal of Medicine on May 12, 2011 (Ex. 1003). I understand that Conroy is prior art at least because it was a printed publication before the earliest possible filing date of the '815 Application. In addition, Conroy was cited as prior art by the Examiner in multiple office actions during the prosecution of the '815 Application, which Patent Owner did not contest. (See generally Exs. 1084, 1088, 1097, 1119.)

95. Conroy discloses the FOLFIRINOX regimen consisting of 85 mg/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. 1003 at 1.)

96. Conroy compares this FOLFIRINOX regimen against gemcitabine at a weekly dose of 1000 mg/m² in patients where the primary endpoint was overall survival. (*Id.* at 1, 3.)

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

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

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

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

101. Conroy also reported that in the study for second-line therapy comparing the FOLFIRINOX regimen to gemcitabine, there was no difference in median survival between the FOLFIRINOX group and the gemcitabine group (4.4 months in each group). (*Id.* at 5.) A POSA would not find this surprising. A POSA would understand that second-line patients had already received a prior round of chemotherapy or cancer treatment that failed, meaning the cancer was not eliminated and likely continued to progress. A POSA would understand that the prior round of chemotherapy treatment and progressing cancer would mean that not only was the patient physically weakened (malnourished, fatigued, weakened immune system, etc.) but the cancer being treated had likely mutated and was therefore less susceptible to treatments.

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

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

B. Conroy Protocol (Ex. 1004)

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

105. Conroy Protocol discloses that the oxaliplatin dose should be reduced from 85 mg/m² to 60 mg/m² based on various known toxicities. (Ex. 1004 at 16-18.) As noted above, a POSA would understand that such dose reductions were standard medical practice. These oxaliplatin dose reductions to 60 mg/m² are also consistent with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m² dose and indicate that a significant

portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m² based on various toxicity events.

106. In addition to the Conroy Protocol, a “Supplemental Appendix” was also provided and published as part of the supplemental materials with Conroy (Ex. 1017). This Supplemental Appendix also discloses using 60 mg/m² oxaliplatin. (Ex. 1017 at 3-7.)

C. Mahaseth (Ex. 1005)

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

108. Mahaseth recognized that the “high [response rate] observed with FOLFIRINOX in metastatic disease raises the possibility of using this regimen in earlier-stage disease to downstage tumors for resection.” (Ex. 1005 at 1.) A POSA would understand this to mean that because more cancers responded to FOLFIRINOX as a treatment, it could be used to treat early-stage cancers to shrink them prior to surgery, whereby the tumor would be removed.

109. Therefore, recognizing that FOLFIRINOX has “superior activity” but “increased toxicity,” one of Mahaseth’s objectives was to address toxicity concerns

with FOLFIRINOX. (*Id.* at 1.) As discussed above with respect to Conroy, this was a known concern with FOLFIRINOX and something those in the art were actively working to address, including Mahaseth. (See *id.*)

110. Based on the understanding that the “bolus 5-FU contributes to the toxicity,” Mahaseth investigated a modified FOLFIRINOX regimen in both locally advanced unresectable and metastatic pancreatic cancer patients by discontinuing the 400 mg/m² bolus of 5-FU. (*Id.*) As discussed herein, a POSA would have known that lowering dosages was a common strategy to remedy or address toxicity concerns. The modified FOLFIRINOX regimen in Mahaseth included oxaliplatin 85 mg/m² in water with 5% dextrose intravenously (IV) over 2 hours, LV 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. (*Id.* at 2.) These are the same doses administered in the traditional FOLFIRINOX regimen, with the exception of the 400 mg/m² 5-FU bolus. (*Id.*) In the study, the premedication regimen consisted of intravenous serotonin 5-HT₃ receptor antagonists and dexamethasone (in accordance with standard medical practice). (*Id.*) Patients received a median of 3 cycles of treatment. (*Id.* at 3.)

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

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

113. Second, Mahaseth confirmed that by eliminating the 5-FU bolus, and thereby decreasing the dosage of 5-FU by 400 mg/m², the modified regimen improved on FOLFIRINOX’s overall efficacy. (*Id.* at 4.) For instance, Mahaseth found that the modified regimen resulted in progression-free survival (PFS) of 13.7 months and overall survival (OS) of 17.8 months. (*Id.*) That is an improvement of 7.3 months (PFS) and 6.7 months (OS), respectively.

D. Bayever (Ex. 1006)

114. Bayever *et al.*, entitled “Methods for Treating Pancreatic Cancer using Combination Therapies Comprising Liposomal Irinotecan,” is an International Application published under the Patent Cooperation Treaty (PCT) with an International Publication No. WO 2013/188586 A1 and publication date of December 19, 2013. The inventors are listed as Eliel Bayever, Navreet Dhindsa, Jonathan Basil Fitzgerald, Peter Laivins, Victor Moyo, and Clet Niyikiza. (Ex.

1006 at 1.) Bayever and Fitzgerald are the same named inventors of the '552 Patent. (See Ex. 1001.) I understand that Bayever is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

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

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

117. Bayever proposes and describes treating pancreatic cancer in a human patient by administering “liposomal irinotecan (*i.e.*, irinotecan sucrose octasulfate salt liposome injection, also referred to as “MM-398”) alone or in combination of 5-fluorouracil (5-FU) and leucovorin (together, 5-FU/LV).” (*Id.* at 4.) Bayever indicates that MM-398 is an irinotecan sucrose sulfate liposome injection and is also known as PEP02, as described in the '867 patent. (*Id.* at 9.) The irinotecan

sucrose sulfate liposome contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carboxymethoxy poly ethyleneglycol-2000)-1,2-distearoyl-sn-glycero-3-phospho-ethanolamine (MPEG-2000-DSPE). (*Id.*; Ex. 1024 at 27:46-51, 91:13-18, claim 31.)

118. In one example, Bayever describes administering MM-398 at a dose of 80 mg/m² administering LV at a dose of 200 mg/m² (*l* form, or levoleucovorin) or 400 mg/m² (*l* + *d* racemic form) and administering 5-FU at a dose of 2400 mg/m² every 2 weeks. (Ex. 1006 at 4.) However, Bayever also discloses that for patients homozygous for the *UGT1A1**28 allele, the MM-398 dose should be lowered to 60 mg/m². (*Id.*; see also *id.* at claim 3.) Thus, Bayever discloses administering liposomal irinotecan in the range of 60-80 mg/m². This disclosure would imply to a POSA that, unless genotyping is performed, dosing of liposomal irinotecan should not exceed 60 mg/m², even in the absence of oxaliplatin.

119. Bayever also discloses a phase 3 clinical trial protocol, in which a dose of MM-398 was reduced to 60 mg/m² for the first occurrence of grade 3 or 4 adverse event or febrile neutropenia for patients not homozygous for *UGT1A1**28 (Arm C). (*Id.* at 26-27, 39-42.) This is the same liposomal irinotecan dose as in the Challenged Claims. (*Id.*)

120. Bayever discloses that “there was a 20-fold increase in tumor AUCSN-38 for MM-398 as compared to free irinotecan,” and “[t]he long duration

of exposure allows for prolonged exposure of the slow proliferating cancer cells to the active metabolite as they progress through the cell cycle.” (*Id.* at 20.) Bayever hypothesized that this activity “result[ed] from a reduction in intra-tumoral hypoxia, and the subsequent downstream effects on angiogenesis, metastasis, and the immunosuppressive environment in tumors.” (*Id.*)

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

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

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

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

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

124. Bayever notes that the MM-398 can be administered as an infusion over 90 minutes or over 60 minutes, (*id.* at 5, 6, 13, 26-27, 33 and claims 6, 15), that “5-FU is administered intravenously over 46 hours” and “leucovorin is administered intravenously over 30 minutes,” (*id.* at 5, 6, 13, 26, 55). Bayever states the “MM-398 PK parameters were not significantly changed when combined with 5-FU/LV.” (*Id.* at 21.)

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

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

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

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

129. Bayever states that, “the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy” and “treating the patient results in a positive outcome, wherein the positive outcome is pathologic complete response (pCR), complete response (CR), partial response (PR) or stable disease (SD).” (*Id.* at 5, 16.) Therefore, a POSA would understand that the combination treatment proposed in Bayever was expected to be therapeutically effective, consistent with the POSA’s understanding of the FOLFIRI regimen.

130. I am aware that the Patent Owner, during prosecution of the '851 Application, argued that Bayever was limited to treating pancreatic cancer only as a second-line therapy. (Ex. 1119 at 146.) Patent Owner stated that “Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® (irinotecan liposome injection), which is indicated for the treatment of patients with metastatic adenocarcinoma of the pancreas *after* disease progression following gemcitabine-based therapy — *i.e.*, as a *second-line therapy* for metastatic cancer.” (*Id.* (emphasis in original).) Patent Owner then continued to argue that the POSA would not combine teachings regarding first-line cancer treatments and second-line cancer treatments. (*See id.*) Contrary to these arguments, a POSA would not understand Bayever to be limited to a second-line therapy and would further understand that the disclosures of Bayever contradict this assertion.

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

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

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

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

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

In another aspect, a method for treatment of pancreatic cancer in **a patient** is provided, the method comprising co-administering to **the patient** an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle of administration, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1 *28 allele on day 1 of each cycle at a dose of 80 mg/m², and to patients homozygous for the UGT1A1 *28 allele on day 1 of cycle 1 at a dose of 60 mg/m² and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m² to 80 mg/m² (e.g., 60 mg/m² or 70 mg/m² or 80 mg/m²);

(b) 5-FU is administered at a dose of 2400 mg/m²; and

(c) leucovorin is administered at a dose of 200 mg/m² (l form) or 400 mg/m² (l+d racemic form).

(*Id.* (emphasis added))

134. Furthermore, under Combination Therapy (Section VI), Bayever goes on to describe various combinations of MM-398, dose adjustments, and dosing orders, but never limits the combinations to second-line therapy. (*Id.* 14.)

Similarly, under Treatment Protocols (Section VII), Bayever describes various treatment combinations but again never once limits these protocols to second-line therapy. (*Id.* at 15.) Moreover, six out of seven working examples, including *in vivo* tumor modeling and Phase I Dose Escalation Studies are not limited to second-line therapy. (*Id.* at 19-25.) While in a single example, Bayever discloses a proposed Phase III clinical trial study design for second-line therapy for pancreatic cancer patients, a POSA in view of the totality of Bayever's disclosure would have known that the disclosed methods were not intended to be nor were they actually limited to second-line therapy.

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

3. A method of treating pancreatic cancer in a human patient, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) **liposomal irinotecan** is administered to patients not homozygous for the *UGT1A1**28 allele on day 1 of each cycle at a dose of 80 mg/m² and to patients homozygous for the *UGT1A1**28 allele on day 1 of cycle 1 at a dose of 60 mg/m² and on day 1 of each subsequent cycle at a dose of 60 mg/m² or 80 mg/m²;

(b) **5-FU** is administered at a dose of **2400 mg/m²**; and

(c) **leucovorin** is administered at a dose of **200 mg/m² (*l* form)** or **400 mg/m (*l* + *d* racemic form)**.

(*Id.* at claim 3 (emphasis added).)

136. In further support of the above discussion, several patents arising out of the Bayever patent family, including U.S. Patent Nos. 9,364,473 and 9,492,442, contain method of treatment claims that are not limited to second-line therapy for

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

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

E. Saif (Ex. 1007)

138. Saif, entitled “MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastasis Pancreatic Cancer,” was authored by Dr. Muhammad Wasir Saif of Tufts University School of Medicine, and published online in the Journal of the Pancreas on May 2014 (Ex. 1007). I understand that Saif is prior art at least because it was a

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

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

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

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

2. Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment. [internal footnotes omitted].

3. It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398. However, bone marrow toxicity has to be borne in mind.

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

F. Ko (Ex. 1008)

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

143. Ko, like other prior art references, evaluated liposomal irinotecan MM-398 (aka PEP02) as a treatment for pancreatic cancer. (Ex. 1008 at 1.) Ko administered MM-398 at a dose of 120 mg/m² that was diluted in 500 ml of 5% dextrose and delivered as a 90-min intravenous infusion every three weeks as a monotherapy for patients with metastatic pancreatic cancer. (*Id.* at 1-2.) Ko disclosed that dose adjustments were made according to toxicities, which included

decreasing the dose of PEP02 to 80 mg/m². (*Id.*) Ko further disclosed the use of premedications, including dexamethasone and a serotonin antagonist. (*Id.*)

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

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

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

Additional studies may explore this drug’s potential role in the ***first-line setting*** and as part of combination regimens for APC. Moreover, given the emergence of ***FOLFIRINOX as a front-line standard in patients with good performance status***, the utility of PEP02 [MM-398] in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

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

G. Conroy 2013 (Ex. 1041)

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

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

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

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

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

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

H. Masi (Ex. 1012)

152. Masi *et al.*, entitled “First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI):

results of a phase II study with a simplified biweekly schedule,” was published in the *Annals of Oncology* in 2004 (Ex. 1012). I understand that Masi is prior art at least because it was a printed publication before the earliest possible claimed priority date of the '815 Application.

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

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

administration, with slightly reduced doses of irinotecan and oxaliplatin and a continuous infusion (rather than a chronomodulated infusion) of 5-FU. (*Id.*)

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

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

I. Ginocchi (Ex. 1016)

157. Ginocchi *et al.*, entitled “Modified FOLFOXIRI In Advanced Pancreatic Cancer,” was published in the *Annals of Oncology* in September 2012 (Ex. 1016). I understand that Ginocchi is prior art at least because it was a printed publication before the earliest possible claimed priority date of the ’815 Application.

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

J. Carnevale (Ex. 1013)

159. Carnevale *et al.*, entitled “MM-398 (Nanoliposomal Irinotecan): Emergence of a Novel Therapy for the Treatment of Advanced Pancreatic Cancer,” was published online in *Future Oncology* on December 21, 2015 (Ex. 1013). I understand Carnevale is prior art at least because it is a printed publication before

this effective filing date if the effective filing date of the '552 patent is deemed to be no earlier than November 10, 2017.

160. Carnevale reviews then recent developments of administering liposomal irinotecan MM-398 in the clinical setting. After discussing MM-398's improved safety, toxicity, and pharmacokinetic properties over standard irinotecan and its FDA approval under the name Onivyde for use in combination with 5-FU and leucovorin for second-line treatment of pancreatic cancer patients, Carnevale concludes that:

It is also of interest whether the optimized PK and safety profile of MM-398 over standard irinotecan would make it **an ideal substitute** for irinotecan in the first-line FOLFIRINOX regimen. This might represent **a natural extension** of MM-398's role in metastatic pancreatic cancer.

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

K. Dean (Ex. 1014)

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

162. Dean is an abstract that reports an open-label phase 2 trial to determine the efficacy and safety of liposomal irinotecan MM-398 with 5-FU, leucovorin, and oxaliplatin in first-line therapy of pancreatic cancer patients. (Ex. 1014 at 2-3.) Dean notes that FOLFIRINOX had emerged as the standard of care for first-line treatment of metastatic pancreatic cancer. Dean also discloses the FDA clinical trial protocol number NCT02551991. (*Id.* at 3.)

L. Additional Prior Art and References

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

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

164. As noted above, I reviewed the file history. In response to a rejection, the alleged inventors argued that there were unexpected results for the claimed regimen. I understand that the legal requirement for unexpected results is a difference in kind (rather than simply a difference in degree), and that the results would have been unexpected to a POSA. In my opinion, there is not only no difference in kind, but no difference in degree. Furthermore, since the prior art

suggested that the claimed formulation was superior to unencapsulated irinotecan, a POSA would have expected the claimed regimen to be superior to the prior art FOLFIRINOX regimen, as that was the POSA's motivation for developing the claimed regimen. I also understand that an inquiry regarding unexpected results is not limited to prior art, or even art available at the time of patent allowance but is an objective inquiry of all available evidence. Thus, I have reviewed recent literature on this topic, which supports my opinion that the patentees' assertion during patent prosecution is not supported by the totality of the evidence. Two recent review articles are consistent with my opinion.

a. Nichetti (Ex. 1010)

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

166. Nichetti evaluated data from phase 3 clinical trials that investigated NALIRIFOX (which is an embodiment of the claims of the '552 patent and is a four-drug combination of liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin), FOLFIRINOX (a prior art regimen, which is a four-drug combination of irinotecan, oxaliplatin, 5-FU, and leucovorin), and GEM-NABP (a combination of gemcitabine and nab-paclitaxel) as first-line treatment of metastatic pancreatic

cancer to compare their reported overall survival (OS) and progression-free survival (PFS). (Ex. 1010 at 1.)

167. Nichetti reported that there was “**no difference observed**” in overall survival between NALIRIFOX (11.1 months) and FOLFIRINOX (11.7 months), and “[a]nalysis of 6- and 12-month OS did not find statistically significantly higher OS for NALIRIFOX compared with FOLFIRINOX.” (*Id.* at 1, 5.) Nichetti further states:

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

(*Id.* at 9 (emphasis added).)

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

b. Nevala-Plagemann (Ex. 1011)

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

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

Table 1 | Key features of NALIRIFOX versus FOLFIRINOX

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

^aApproximate average wholesale cost for nanoliposomal irinotecan or irinotecan for a patient with a body surface area of 2.0 m². ^bNo central review of images. ^cPrimary prophylaxis with granulocyte colony-stimulating factor was encouraged in NAPOLI 3 and not recommended in PRODIGE 4. ^dIncludes peripheral neuropathy and peripheral sensory neuropathy⁸. AE, adverse event; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; mOS, median overall survival; mPFS, median progression-free survival; NALIRIFOX, nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin; ORR, objective response rate.

IX. OVERVIEW OF THE '552 PATENT

A. The Specification and Claims of the '552 Patent

171. I have read the '552 Patent, titled “Methods for treating metastatic pancreatic cancer using combination therapies comprising liposomal irinotecan and oxaliplatin,” and reviewed the relevant portions of the prosecution history of the '552 patent. The '552 patent issued from U.S. Non-Provisional Patent Application No. 15/809,815 (“the '815 Application”), filed on November 10, 2017, which is a continuation of U.S. Non-Provisional Patent Application No. 15/241,106, filed August 19, 2016 (“the '106 Application”), which claims the benefit of priority to U.S. Provisional Application No. 62/208,209 filed August 21, 2015 (“the '209 Provisional”), U.S. Provisional Application No. 62/216,736 filed September 10, 2015 (“the '736 Provisional”), U.S. Provisional Application No. 62/273,244 filed December 30, 2015 (“the '244 Provisional”), U.S. Provisional Application No. 62/281,473 filed January 21, 2016 (“the '473 Provisional”), U.S. Provisional Application No. 62/302,341 filed March 2, 2016 (“the '341 Provisional”), U.S. Provisional Application No. 62/323,245 filed April 15, 2016 (“the

'245 Provisional”), and U.S. Provisional Application No. 62/343,313 filed May 31, 2016 (“the ’313 Provisional”). (Ex.1001 at 1:9-17.) The entire contents of which are incorporated herein by reference. The ’552 patent lists Eliel Bayever, Sarah F. Blanchette, Jonathan Basil Fitzgerald, Daniel F. Gaddy, Bart S. Hendriks, Ashish Kalra, and Helen Lee as the inventors and Ipsen Biopharm Ltd as the Assignee.

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

173. The ’552 patent states that,

The invention is based in part on several pre-clinical discoveries. First, liposomal irinotecan improved anti-tumor activity of the topoisomerase I inhibitor SN-38 (an active metabolite of irinotecan) relative to exposure-matched doses of non-liposomal irinotecan. Second, liposomal irinotecan combined with 5-fluorouracil and oxaliplatin consistently improved tumor growth inhibition and survival in mouse

xenograft models of pancreatic cancer relative to non-liposomal irinotecan, without exacerbating the baseline toxicities of these agents.

(*Id.* at 2:47-57.)

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

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

regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398's superior PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the efficacy of FOLFIRINOX)." (*Id.* at 21:50-56.) Example 4 describes the results of a phase 1 trial of a treatment regimen combining liposomal irinotecan, 5-FU/LV, and oxaliplatin. While the Example clearly describes administration of three different dosing regimens to patients with previously untreated pancreatic cancer, it does not describe any therapeutic benefit (clinical efficacy) in any patients. Example 5 is a description of ONIVYDE® (Irinotecan Liposome Injection) Liposomal Irinotecan. (*Id.* at 43: 21-46:61.) None of these examples suggests to a POSA that the inventors recognized that they possessed a method of treating metastatic pancreatic cancer patients with any therapeutic benefit (clinical efficacy).

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

177. Independent claim 1 recites:

A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m² of liposomal irinotecan,

b. 60 mg/m² oxaliplatin,

c. 200 mg/m² of the (1)-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.

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

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

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

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

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

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

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

185. Claim 9 depends from claim 1 and recites, “the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxy polyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).”

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

187. Claim 11 depends from claim 10 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

188. Independent claim 12 recites:

A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (1)-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.

189. Claim 13 depends from claim 1 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

190. Claim 14 depends from claim 12 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal

irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

191. Claim 15 depends from claim 1 and recites, “each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.”

B. The Prosecution History of the '552 Patent

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

A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 or 85 mg/m² oxaliplatin,
- c. 200 mg/m² of (*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. 1084 at 60.)

193. Claim 16 recited:

A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

a. 60 mg/m² of liposomal irinotecan,

b. 85 mg/m² oxaliplatin,

c. 200 mg/m² of (*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.

(*Id.* at 61.)

194. Claim 19 recited:

A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of (*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.

(*Id.* at 63.)

195. On March 6, 2018, the Patent Office issued a Non-final Office Action, rejecting the claims for, among other rejections, obviousness. (Ex.1084 at 192.) Claims 1-3, 5-8, 10, 16 and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever *et al.* (WO 2013/188586) (“Bayever”), in view of Conroy *et al.* (N Engl J Med. 2011 May 12;364(19):1817-25) (“Conroy”). (*Id.*) Claims 4, 9, and 18 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Fleming *et al.* (<https://www.oncologynurseadvisor.com/features/importance-of-sequence-in-chemotherapy-administration/>) (“Fleming”). (*Id.* at 194-195.) Claims 11-15, 17, and 20 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Melis and as evidenced by Bayever *et al.* (WO 2016/094402) (“Bayever II”). (*Id.*) Claims 1-20 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U S. Patent No. 9,492,442 (“’442 patent”), in view of Conroy. (*Id.* at 196.)

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

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
 - a. 60 mg/m² of liposomal irinotecan,
 - b. 60 ~~or 85~~ mg/m² oxaliplatin,
 - c. 200 mg/m² of (*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.

(*Id.* at 287.)

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

198. On September 11, 2018, the Patent Office issued a Final Office Action, rejecting the claims for, among other rejections, obviousness. (*Id.* at 314-27.) Claims 1-3, 5-8, 10, and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Alcindor *et al.* (Curr Oncol. 2011 Jan;18(1):18-25) (“Ex. 1027”). (*Id.* at 316.) Claims 1, 4-15,

18-19, and 21-22 were rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of the '442 patent, in view of Conroy and further in view of Alcindor. (*Id.* at 323.)

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

200. On July 8, 2019, the Patent Office issued a Non-Final Office Action, rejecting the claims for, among other rejections, obviousness. (Ex. 1088 at 59.) Claims 1-3, 5-8, 10, and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Melis *et al.* (The Society for Surgery of the Alimentary Tract; 52nd Annual Meeting Posters, May 6 - 10, 2011; <http://meetings.ssat.com/abstracts/11ddw/P57.cgi>) (“Melis”). (*Id.*) Claims 4, 9, 18, and 23 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Melis and further in view of Fleming. (*Id.*, 62.) Claims 11-15 and 21-22 were rejected under 35 U.S.C. § 103 as being unpatentable over Bayever in view of Conroy and further in view of Melis and as evidenced by Bayever II. (*Id.*, 64.) Claims 1, 4-15, 18-19, and 21-23 are rejected on the ground of nonstatutory double patenting as being

unpatentable over claims 1-18 of the '442 patent, in view of Conroy and further in view of Melis. (*Id.*, 65.)

201. In its response dated January 7, 2020, the Applicant made a minor amendment to independent claims 1 and 19 to recite “200 mg/m² of the (*l*) form of leucovorin or 400 mg/m² of the (*l+d*) racemic form of leucovorin.” (Ex. 1091 at 350-352.)

202. In the Final Office Action dated February 27, 2020, the Patent Office maintained the rejections against claims 1, 5-8, 10, and 19 under 35 U.S.C. § 103 as being unpatentable over Bayever, in view of Conroy and further in view of Melis. (Ex. 1097 at 190-195.) The Patent Office also maintained the rejections against claims 4, 9, 18, and 23 under 35 U.S.C. § 103 as being unpatentable over Bayever, Conroy, in view of Melis and further in view of Fleming. (*Id.* at 195-197.) The Patent Office further maintained the rejections against claims 11-15 and 21-22 under 35 U.S.C. § 103 as being unpatentable over Bayever, Conroy, in view of Melis and as evidenced by Bayever II. (*Id.* at 197-199.) Finally, the Patent Office maintained the rejections against claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of the '442 patent, in view of Conroy and further in view of Melis. (*Id.* at 200-201.)

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

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~:

- a. 60 mg/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.

19. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~:

- a. 60 mg/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. 1098 at 212-214.)

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

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

206. First, Patent Owner admitted, throughout prosecution, that Bayever discloses a treatment of pancreatic cancer by administering a combination of

liposomal irinotecan (*e.g.*, 60 or 80 mg/m²), in combination with LV (*e.g.*, 400 mg/m² *l+d* form) and 5-FU (*e.g.*, 2,400 mg/m²) to a patient once every two weeks. (See Ex. 1084 at 292.) Patent Owner also repeatedly admitted that Conroy discloses administering to patients with first-line metastatic pancreatic cancer, a combination of 85 mg/m² of oxaliplatin, 180 mg/m² non-liposomal irinotecan, 400 mg/m² LV, 400 mg/m² 5-FU as bolus injection followed by 2,400 mg/m² 5-FU as a continuous infusion once every two weeks. (See *id.* at 292, 381.)

207. Patent Owner argued, however, that there was no motivation to combine these references (with each other or other references). Patent Owner’s first argument was that neither Bayever nor Conroy taught co-administration of 60 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin. (Ex. 1119 at 145.)

Differences between Conroy and Claim 1 as articulated by Patent Owner are reproduced below but with an inclusion of Bayever’s admitted disclosures:

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

208. Patent Owner focused on the references individually—instead of what was more broadly known or understood by the POSA—to argue there is “no mention of any liposomal irinotecan *in Conroy* or adjusting any of the dosages *in*

Conroy” to arrive at the claimed subject matter. (*Id.* (emphasis added).) Similarly, Patent Owner argued that “nowhere does Bayever teach or suggest incorporating oxaliplatin into its therapeutic regimen.” (*Id.*) Patent Owner further argued there was also no basis to combine because there is “no basis to combining teachings regarding second-line therapy with teachings regarding first-line therapy” and claimed Bayever’s teachings are only for second-line treatment and Conroy’s are only for first-line treatment. (*Id.* at 146.)

209. Despite admitting that Melis discloses the use of 60 mg/m² of oxaliplatin in the treatment of advanced pancreatic cancer and acknowledging that Conroy discloses the use of oxaliplatin (at a higher dose) with irinotecan, leucovorin, and 5-FU, Patent Owner argued there is no evidence that it was obvious to try using 60 mg/m², and thus combine the art, because **Melis** did not disclose such use with irinotecan or leucovorin and **Melis** did not recognize predictable outcomes of coadministration, *e.g.*, tolerability or efficacy. (*Id.* at 146-147.) That is, Patent Owner again focused on each reference in isolation and ignored the teachings of other art known to a POSA, *e.g.*, Patent Owner ignored that Conroy’s disclosure of a dose of oxaliplatin of at least 60 mg/m² showed such tolerability.

210. Second, Patent Owner argued a POSA had no reasonable expectation of success in combining the references. Patent Owner argued that a POSA could

not expect “a reasonable expectation of similar results” in combining teachings of first- and second-line treatments and because there was no comparison of liposomal vs. non-liposomal irinotecan. (*Id.* at 148-49.) Patent Owner argued a POSA would not have been motivated to use a different (lower) dose of oxaliplatin and argued that such a combination was not tolerable, but the only alleged support for this comes from a post-filing paper. (*Id.* at 149-50.)

211. Finally, Patent Owner argued that the claimed subject matter produced unexpected results. Patent Owner relies on a 2020 paper to argue that of different dosages, only the claimed dosage was purportedly tolerable and had efficacy outcomes higher than FOLFORINX. (*Id.* at 152-53.) In relying on the post filing Wainberg references (Wainberg Z, *et al.*, Ann Oncol. 31 (Suppl 3):S241 (2020) (“Wainberg abstract”); corresponding poster (“Wainberg poster”) and presentation (“Wainberg presentation”)) (Ex 1018) purported to show unexpected results, Patent Owner argued that Wainberg showed that the claimed dose of 60 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin (60/60) was more tolerable than regimens with higher doses of either liposomal irinotecan or oxaliplatin. (Ex. 1119 at 153; Ex. 1018.)

212. On April 11, 2022, the Patent Office issued a Notice of Allowance without stating specific reasons for allowance, and indicated that claims 1, 4-13,

19, and 21-23 were allowed, and claims 14, 15, and 18 were canceled. (Ex.1123 at 461-63.)

213. During prosecution, it is my understanding that Patent Owner submitted over 1,000 references in a total of thirty-six Information Disclosure Statements (“IDSs”): submitting an IDS on August 6, 2018, three on February 11, 2019, four on February 13, 2019, four on January 7, 2020, four on January 9, 2020, seven on February 25, 2021, six on March 12, 2021, one on May 26, 2021, one on March 9, 2022, four on March 10, 2022, and one on March 11, 2022. Mahaseth, Ko, Cantore, and Dean were disclosed as part of 242 total disclosures identified by the Patent Owner between February 11-13, 2019. Conroy 2013, Saif, Masi, Ginocchi, and Carnevale were not disclosed or considered during prosecution. (Of course, Nichetti and Nevala-Plagemann had not yet been published.)

C. The Priority Date of the ’552 Patent

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

215. I am told that to establish priority, the earlier application must describe the later-claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought—which I understand to mean that the earlier disclosure must describe and enable the later-claimed invention with all of its limitations. I further understand that a plan to obtain or achieve the claimed invention in the future is insufficient to show possession at the time of filing.

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

217. Neither the multiple provisional applications nor the ’106 Application, to which the ’552 patent claims priority, describe data showing efficacy of the claimed regimen in a human study. Indeed, all the provisional applications and the ’106 Application only contain a phase 2 study protocol to assess, in the future, the

preliminary efficacy and safety of the Nal-IRI (also referred to as MM-398), oxaliplatin, LV, and 5-FU regimen. (See, *e.g.*, Ex. 1015 at Example 1; Ex. 1028 at Example 1; Ex. 1029 at Example 1; Ex. 1030 at Example 1; Ex. 1031 at Example 1; Ex. 1032 at Example 1; Ex. 1060 at Example 1; Ex. 1020 at Example 3.)

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

219. Specifically, the '209 Provisional proposed a “***study to assess the preliminary efficacy and safety***” of the following “in previously untreated metastatic pancreatic cancer patients ***to assess the most promising regimen for***

further development:” (1) “***nal-IRI + 5-FU/LV + oxaliplatin***” and (2) “nal-IRI + 5-FU/LV.” (*Id.* at ¶ [00112] (emphasis added).) These two regimens were to be compared to nab-paclitaxel + gemcitabine. (*Id.* at ¶ [00122].) The regimens were as follows:

- i. nal-IRI + 5-FU/LV + oxaliplatin (Arm 1)
- ii. nal-IRI + 5-FU/LV (Arm 2)
- iii. nab-paclitaxel + gemcitabine (Arm 3)

(*Id.*)

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

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

222. Importantly, Arm 1 is described as comprising nal-IRI (administered at 80 mg/m²), then oxaliplatin (administered in doses ranging from 60-85 mg/m²), then LV (*l + d* form, administered at 400 mg/m²), and finally 5-FU (administered at 2400 mg/m²). (*Id.* at ¶¶ [00146]-[00153].) The study design contemplated that the oxaliplatin dose would be reduced (from 85 mg/m² to 60 mg/m²) for at least some patients, including to test for unexpected toxicities. (*Id.* at ¶ [00277].) The nal-IRI dose was also contemplated as being reduced (from 85 mg/m² to 60 mg/m²) if, *e.g.*, a patient was known to be homozygous for *UGT1A1**28, present in approximately 10% of Caucasians. (*Id.* at ¶¶ [0061], [00264].) These reduced doses would also be administered upon agreement of the Investigators, the Sponsor, and the Medical Monitor. (*Id.* at ¶ [00288].)

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

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

225. That is, a POSA would have understood from each of the seven provisional applications and from the '106 Application that the Patent Owner had created a study protocol to test, at some point in the future, the efficacy, safety, and tolerability of a drug combination including nal-IRI or MM-398 (administered at 80 mg/m²), then oxaliplatin (administered in doses ranging from 60-85 mg/m²), then LV (*l + d* form, administered at 400 mg/m²), and finally 5-FU (administered at 2400 mg/m², *i.e.*, Arm 1. Therefore, a POSA would know that the Patent Owner had no real data, only hypotheses, as to what the efficacy, safety, or tolerability of such a treatment would be at the time it filed any one of these applications.

226. In addition, nowhere in any of the applications to which the '552 Patent claims priority is any suggestion that a patient had actually received the treatment claimed in the '552 Patent, *i.e.*, a treatment of 60 mg/m² liposomal irinotecan, 60 mg/m² oxaliplatin, 400 mg/m² LV *l + d* form (or 200 mg/m² (*l*)-form), and 2400 mg/m² 5-FU. Therefore, not surprisingly, there are also no data about the actual efficacy, safety, or tolerability of the treatment.

227. Therefore, it is my opinion that a POSA would not recognize that the inventors of the '552 Patent had possession of the claimed invention based on any priority claim made. Therefore, it is my opinion that a POSA would recognize that the '552 Patent's priority claim, *i.e.*, any possession of the claimed subject matter,

cannot be made to anything earlier than November 10, 2017, which is the date the '815 Application was filed.

X. UNPATENTABILITY OF THE '552 PATENT

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

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

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

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

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

231. Independent claim 1 recites:

Claim 1: A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (1)-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.

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

233. The FOLFIRINOX regimen as first described by Conroy *et al.* consists of 85 mg/m² oxaliplatin, 180 mg/m² irinotecan, 400 mg/m² leucovorin, and 5-FU, first administered as a 400 mg/m² bolus and then 2400 mg/m² 5-FU infusion, administered every two weeks in first-line therapy in patients with metastatic pancreatic cancer. (Ex. 1003 at 1.)

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

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

(emphasis added).) As with Saif, Ko also suggested that given the emergence of FOLFIRINOX as a first-line standard in advanced pancreatic cancers, MM-398 should be further explored in the first-line therapy setting. (Ex. 1008 at 5.)

236. In addition, Bayever suggests such a substitution and provides even further motivation to combine, as Bayever and other prior art disclosed evidence of superiority of liposomal irinotecan to irinotecan. (See Ex. 1006 at 11, 19-21, 25; Ex. 1008 at 2-5; Exs. 1058-1059.) Bayever suggests its liposomal formulation of irinotecan “has several attributes that may provide an improved therapeutic index,” therapeutic synergy, or “superior outcome.” (*Id.* at 5, 10, 16.) Bayever disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims (60 mg/m²) along with the same claimed doses of leucovorin (*i.e.*, 200 mg/m² of the (1)-form or 400 mg/m² of the (1+d) racemic form) and 5-FU (*i.e.*, 2,400 mg/m²). (*Id.* at 4, 6, 14-15, 26-27, 32-33, 39-42, 54, 63.)

237. Bayever disclosed that MM-398 administration results in a 20-fold increase in tumor AUC_{SN-38} for MM-398 compared to free irinotecan. (*Id.* at 20.) The long duration of exposure allows for prolonged exposure of the slow-proliferating cancer cells to the active metabolite SN-38 as they progress through the cell cycle. (*Id.*) Bayever also disclosed that MM-398 has several attributes that may provide an improved therapeutic index, including local bioactivation that

results in reduced drug exposure at potential sites of toxicity, increased exposure at cancer cells within the tumor, and potentially greater susceptibility of tumors to agents such as 5-FU/LV. (*Id.* at 20-21.)

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

and listing several purported advantages of MM-398 suggesting the superiority of MM-398 and that it works better than free irinotecan).)

239. A POSA would have therefore been motivated to replace free irinotecan in the FOLFIRINOX regimen with liposomal irinotecan. Bayever discloses doses of 80 mg/m² liposomal irinotecan in some regimens but recommends lowering that dose to 60 mg/m² for those with toxicity concerns, including for patients homozygous for the *UGT1A1**28 allele. (Supra Sections VII.D.c; VIII.E.) Therefore, a POSA would have understood that doses of liposomal irinotecan in the range of 60-80 mg/m² were tolerable in most patients but that 80 mg/m² was probably not tolerable in patients homozygous for the *UGT1A1**28 allele (as well as other known poor metabolizer alleles).

240. A POSA would have found any dose within the 60-80 mg/m² an obvious option for future study. In addition, a POSA—with an aim to reduce toxicity of the FOLFIRINOX regimen, as taught by at least Conroy, Conroy Protocol, and Conroy 2013—would have certainly considered a starting dose of 60 mg/m² as taught by Bayever. (See Ex. 1006 at 4; Sections VIII.A-C, E.) This is consistent with the dose reduction of MM-398 to 60 mg/m² by Bayever when patients experience an adverse event. (Ex. 1006 at 39-42.)

241. Second, given the toxicity of FOLFIRINOX, a POSA would be motivated to also lower the 85 mg/m² dose of oxaliplatin to reduce toxicity

concerns. Notably, Conroy and Conroy Protocol taught the potential need for reduction of the oxaliplatin dose. For example, Conroy disclosed that a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m² oxaliplatin was used in the study, indicating in many patients a lower dose of oxaliplatin was administered. (Section VIII.A; Ex. 1003 at 4.) The Conroy Protocol also disclosed a dose reduction of oxaliplatin to 60 mg/m² oxaliplatin for toxicity. (Ex. 1004 at 16-18, 27.) A POSA who reviewed the results of Conroy stating that the median dose intensity of oxaliplatin was 78% and the fact that the Conroy Protocol disclosed numerous dose reductions of oxaliplatin to 60 mg/m² oxaliplatin in the event of certain toxicity incidents would have concluded that a significant portion of patients undergoing the FOLFIRINOX trial were administered oxaliplatin 60 mg/m². In addition, because a POSA would have been motivated to substitute MM-398 for the free irinotecan in FOLFIRINOX, an effective but toxic regimen, a POSA would have been cautious about oxaliplatin dosing. A POSA would therefore have considered lowering the oxaliplatin dose through routine optimization.

242. Based on the disclosures in the prior art, a POSA would have understood that doses of oxaliplatin in the range of 60-80 mg/m² were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m² FOLFIRINOX dose. Because most dosing is done in

increments of 5 mg/m², a POSA would have a limited number of tolerable doses to choose from and found any dose within that range an obvious choice. In addition, a POSA would have been aware of the 60 mg/m² dose of oxaliplatin disclosed in the Conroy protocol. (See Section VIII.B.) A POSA would have been motivated to select a dose that had already been used or tested. (See *id.*; see also Section VIII.H (also disclosing a 60 mg/m² dose of oxaliplatin). Moreover, a POSA would have understood that other art, like Cantore, showed or suggested that these lower dose regimens, including a 60 mg/m² dose of oxaliplatin along with 60 mg/m² irinotecan, were found to be safe and effective in metastatic pancreatic cancer patients.

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

244. Third, a POSA would also have known that a modification of the 5-FU dose would also improve the toxicity profile. Specifically, a POSA would have known of Mahaseth *et al.* (and others, as reviewed in Conroy 2013) who developed a modified FOLFIRINOX regimen by discontinuing the 400 mg/m² bolus of 5-FU from the FOLFIRINOX regimen. (Ex. 1005 at 2). This modified regimen was well

tolerated and improved the safety profile of the original FOLFIRINOX regimen with respect to neutropenia, fatigue, and vomiting. (*Id.* at 4.) It also maintained FOLFIRINOX’s overall efficacy, with progression-free survival (PFS) and overall survival (OS) of 13.7 and 17.8 months, respectively. (*Id.*) Mahaseth concluded that this “modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC (pancreatic cancer).” (*Id.* at 5.) A POSA would have been motivated to reduce Conroy’s 5-FU dose to achieve these same benefits.

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

Claim 1 of the '552 patent	Prior Art
1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: a. 60 mg/m² of liposomal irinotecan, b. 60 mg/m² oxaliplatin, c. 200 mg/m² of the (<i>l</i>)-form of leucovorin or 400 mg/m² of the (<i>l</i>+<i>d</i>) racemic form of leucovorin, and	Conroy, Conroy Protocol, and Mahaseth disclose: The FOLFIRINOX method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: 180 mg/m² irinotecan, 85 mg/m² oxaliplatin,

Claim 1 of the '552 patent	Prior Art
d. 2,400 mg/m² 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.	400 mg/m² of the (<i>l+d</i>) racemic form of leucovorin, and 2,400 mg/m² 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient. Bayever discloses: A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: 60 mg/m² of liposomal irinotecan, 400 mg/m² of the (<i>l+d</i>) racemic form of leucovorin, and 2,400 mg/m² 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.

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

247. I am also aware of the unexpected result arguments put forth by the applicant of the '552 patent during prosecution. (Ex. 1119 at 151; see also Section

IX.B (discussing alleged unexpected results and reliance on post-filing Wainberg reference).)

248. However, as explained herein, such a result is hardly unexpected. Since it has been universally accepted in the prior art that providing lower doses of these chemotherapy drugs, including oxaliplatin, would result in fewer side effects, a POSA would have expected that the claimed doses of 60 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin (60/60) would confer better safety and tolerability than doses of 60 mg/m² liposomal irinotecan and 85 mg/m² oxaliplatin (60/85) as suggested by Conroy and Conroy Protocol in view of Mahaseth and Bayever.

249. Wainberg merely reveals that the 60/60 regimen was selected because it showed one less patient (one out of seven) exhibiting a dose limiting toxicity (DLT) over the 60/85 regimen (two out of ten). (Ex. 1018 at 19). No POSA would consider the difference between the 60/60 regimen and the 60/85 regimen to be a difference in kind, as the difference is most likely attributable to chance rather than any difference in DLT.

250. Patent Owner then argued that the 60/60 regimen “unexpectedly resulted in primary efficacy outcomes higher than that of the currently preferred FOLFIRINOX regimen as reported in Conroy” and concluded “[t]hese improvements are tangible benefits that demonstrate an improvement in efficacy of

the claimed dosage regimens over the Conroy FOLFIRINOX regimen.” [Ex. 1119 at 153 (emphasis added)]. However, as I explained below, this argument regarding efficacy outcomes is seriously flawed.

251. First, Wainberg *et al.* (Wainberg, *et al.*, European Journal of Cancer, 151:14-24 (2021)) (“Wainberg 2021” (Ex. 1019)) made it clear that no such comparisons can be made between its results and those of FOLFIRINOX because of the inherent limitations of its study. In fact, Wainberg *et al.* stated that they “cannot be reliably compared with that of established therapies without head-to-head studies,” and that “direct comparisons” between the two studies “cannot be made,” especially in view of the “[l]imitations inherent in [Wainberg’s] study design includ[ing] the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomized design; and the absence of a control group.” (Ex. 1019 at 8.) Wainberg highlights that “important differences between the study populations include the proportions of patients with metastatic disease at study entry..., the proportions with liver metastases..., and the median ages,” where the FOLFIRINOX patients were older and had a higher proportion of metastatic disease. (*Id.*) The statements by Wainberg teach a POSA that any apparent differences may be due to chance, and therefore certainly could not be considered a difference in kind.

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

253. Similarly, Nevala-Plagemann states that in comparison with the PRODIGE 4 (containing a FOLFIRINOX arm), “NALIRIFOX does not seem to raise the bar, but rather exposes patients and health-care systems to financial toxicities,” and “A recently published systematic review and meta-analysis supports our conclusion that the differences in OS between NALIRIFOX and modified FOLFIRINOX are not clinically significant and that those in neuropathy are not statistically significant.” (Ex. 1011 at 1, 2 (emphases added).) More specifically, Nevala-Plagemann reports that the “median OS [overall survivability]

of patients receiving NALIRIFOX in NAPOLI 3 is identical to that of those who received FOLFIRINOX in PRODIGE 4 (11.1 months).” (*Id.* at 567 (emphasis added).) With regard to toxicity, Nevala-Plagemann further states “6.5% of patients receiving NALIRIFOX had grade ≥ 3 peripheral neuropathy (3% peripheral neuropathy and 3.5% peripheral sensory neuropathy) compared to 9% of patients receiving FOLFIRINOX in PRODIGE 4, a clinically insignificant difference.” (*Id.* at 2 (emphasis added).)

254. Importantly, a POSA would recognize that Nichetti and Nevala-Plagemann do not share the inherent limitations of Wainberg (relied upon during prosecution) because their analyses are more comprehensive, and not focused on a single clinical trial. Moreover, Nichetti and Nevala-Plagemann clearly refute Patent Owner’s argument that the regimen of the claims of the ’552 patent exhibited unexpected results, at least because the claimed regimen yielded identical or clinically insignificant efficacy differences as compared to the prior art FOLFIRINOX first-line therapy.

255. Finally, even if the claimed regimen were deemed to be in some way superior to the closest prior art (FOLFIRINOX, as disclosed in Ex. 1003), a POSA would not have found that result to have been unexpected, since Bayever taught that liposomal irinotecan was superior to free irinotecan, and therefore a POSA would have expected the claimed regimen to be superior to FOLFIRINOX. This

opinion is supported by Saif and Ko, who both were excited about such a substitution, in hopes of improving the overall survival of patients with pancreatic cancer.

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

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

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

b. Claim 3

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

260. Both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (Ex. 1003 at 3; Ex. 1005 at 2.) In addition, Bayever also

discloses “5-FU is administered intravenously over 46 hours.” (Ex. 1006 at 5, 6, 13, 26.)

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

c. Claim 4

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

263. Conroy, Mahaseth, and Bayever all disclose that the LV is administered immediately prior to 5-FU. (Ex. 1003 at 3; Ex. 1005 at 2; Ex. 1006 at 27.) In particular, Bayever discloses “leucovorin should always be administered prior to 5-FU.” (Ex. 1006 at 27 and claim 4). Therefore, it was known to administer LV immediately prior to the 5-FU.

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

d. Claim 5

265. In my opinion, claim 5 of the ’552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 5

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

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

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

e. Claim 6

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

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

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

f. Claim 8

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

272. Bayever discloses MM-398 (also known as PEP02), which is irinotecan sucrose octasulfate encapsulated in liposomes. (Ex. 1006 at 4-7, 9 (stating that “irinotecan is administered in a stable liposomal formulation as irinotecan sucrose sulfate liposome injection (otherwise termed ‘irinotecan sucrose octasulfate salt liposome injection’)).

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

g. Claim 9

274. In my opinion, claim 9 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 9 depends from claim 1 and recites “the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).”

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

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

h. Claim 10

277. In my opinion, claim 10 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claim 1. Claim 10 depends from claim 1 and recites, “the liposomal irinotecan comprises irinotecan

sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carboxymethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).”

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

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

i. Claim 11

280. In my opinion, claim 11 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claims 1, 3-5, and 10. Claim 11 depends from claim 10 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of

the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

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

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

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

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

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

j. Claim 12

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

Claim 12 recites:

12. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (1)-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.

287. A comparison of claim 1 and claim 12 is provided in the chart below.

As shown, claim 12 further specifies an antineoplastic agent as gemcitabine.

Claim 1	Claim 12
1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: a. 60 mg/m² of liposomal irinotecan, b. 60 mg/m² oxaliplatin, c. 200 mg/m² of the (<i>l</i>)-form of leucovorin or 400 mg/m² of the (<i>l</i>+<i>d</i>) racemic form of leucovorin, and d. 2,400 mg/m² 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.	12. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: a. 60 mg/m² of liposomal irinotecan, b. 60 mg/m² oxaliplatin, c. 200 mg/m² of the (<i>l</i>)-form of leucovorin or 400 mg/m² of the (<i>l</i>+<i>d</i>) racemic form of leucovorin, and d. 2,400 mg/m² 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.

288. A POSA would have understood that gemcitabine is an antineoplastic agent, and the FOLFIRINOX regimens of Conroy and Mahaseth were administered as first-line therapy in patients who had not been previously treated with gemcitabine. (Ex. 1003 at 1; Ex. 1005 at 1.) Thus, claim 12 would also have

been obvious to a POSA based on the above discussion with respect to claim 1 and in view of the prior art.

k. Claim 13

289. In my opinion, claim 13 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claims 1 and 11. Claim 13 depends from claim 1 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

290. Conroy discloses that irinotecan, oxaliplatin, 5-FU and LV were administered every two weeks, which corresponds to days 1 and 15. (Ex. 1003 at 3.) Conroy also discloses that six months of chemotherapy was recommended for patients who had a response, which constitutes at least one 28-day treatment cycle. Similarly, Bayever also discloses that liposomal irinotecan MM-398 and leucovorin were also administered at least one cycle with a period of 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated “until

disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (Ex. 1006 at 6, 14, 15, 26-27.)

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

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

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

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

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

I. Claim 14

296. In my opinion, claim 14 of the '552 patent would also have been obvious in view of the prior art as discussed above regarding claims 12, 11, and 13. Claim 14 depends from claim 12 and recites, “the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.”

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

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

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

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

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

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

a. Claim 7

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

administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.”

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

b. Claim 15

304. In my opinion, claim 15 of the '552 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1 of Ground 1 and Ground 2. Claim 15 depends from claim 1 and recites, “each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.”

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

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

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

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

a. Claim 1

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

308. 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.

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

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

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

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

b. Claim 3

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

c. Claim 4

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

d. Claim 5

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

e. Claim 6

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

f. Claim 7

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

g. Claim 8

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

h. Claim 9

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

i. Claim 10

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

j. Claim 11

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

k. Claim 12

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

l. Claim 13

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

m. Claim 14

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

n. Claim 15

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

XI. CONCLUSION

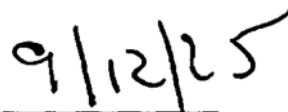
325. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination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

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

Signature: _____


Robert Dreicer, M.D., M.S., MACP, FASCO

Date: _____



Appendix A – Curriculum Vitae

CURRICULUM VITAE

9/9/2025

Robert Dreicer, M.D.,M.S., MACP, FASCO

I. **Personal Data**

A. Citizen Status: U.S.A.

II. **Education**

<u>Year</u>	<u>Degree</u>	<u>Institution</u>
1977	B.S.	Colorado State University, Fort Collins, CO
1979	M.S.	University of Texas Graduate School Biomed Sciences, Houston, Tx
1983	M.D.	University of Texas Medical School at Houston, Houston, Tx

III. **Post-Graduate Education**

<u>Year</u>	<u>Position</u>	<u>Institution</u>
1983-84	Intern in Medicine	Indiana University School of Medicine, Indianapolis,IN
1984-86	Resident in Medicine	Indiana University School of Medicine, Indianapolis,IN
1986-88	Fellow in Oncology	University of Wisconsin Clinical Cancer Center, Madison, WI
1988-89	Research Associate	University of Wisconsin Clinical Cancer Center, Madison, WI

IV. **Academic Appointments**

<u>Year</u>	<u>Position</u>	<u>Institution</u>
1989-90	Associate	Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA
1989-90	Associate	Department of Urology, University of Iowa College of Medicine, Iowa City, IA
1990-95	Assistant Professor	Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA

Academic Appointments (cont)

<u>Year</u>	<u>Position</u>	<u>Institution</u>
1990-95	Assistant Professor	Department of Urology, University of Iowa College of Medicine, Iowa City, IA
1995-99	AD for Clinical Research	University of Iowa Cancer Center, Iowa City, IA
1995-99	Associate Professor	Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA
1995-99	Associate Professor	Department of Urology, University of Iowa College of Medicine, Iowa City, IA
1996-99	Associate Division Director	Division of Hematology/Oncology, Department of Medicine, University of Iowa College of Medicine, Iowa City, IA
1998-99	Interim AD for Clinical Affairs	University of Iowa Cancer Center, Iowa City, IA
1999-2014	Staff Physician	Department of Hematology/Oncology, Cleveland Clinic, Cleveland, OH
1999-2014	Staff Physician	Urologic Institute, Cleveland Clinic Cleveland, OH
1999-2003	Associate Professor	Department of Internal Medicine, Ohio State University, Columbus, Ohio (Academic Appt only)
1999-14	Director- Genitourinary Medical Oncology	Cleveland Clinic, Cleveland, OH
1999-2014	Associate Director	Cleveland Clinic, Cleveland OH
2004-14	Professor of Medicine	Cleveland Clinic Lerner College of Medicine of Case Western University, Cleveland, OH
2006-14	Chairman	Department of Solid Tumor Oncology, Cleveland Clinic, Cleveland, OH

Academic Appointments (cont)

2012-14	Deputy AD for Clinical Research	Case Comprehensive Cancer Center, Cleveland, OH
2015-	Professor Medicine	Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, VA
2015-	Professor of Urology	Department of Urology, University of Virginia School of Medicine, Charlottesville, VA,
2015-	Head Section of Medical Oncology	Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, VA
2015-	Deputy Director	University of Virginia Cancer Center, Charlottesville, VA,
2015-	AD for Clinical Research	University of Virginia Cancer Center, Charlottesville, VA,
2015-	Co-Director Paul Mellon Urologic Cancer Institute	University of Virginia, Charlottesville, VA

V. Certification and Licensure

<u>Board</u>	<u>Date</u>	<u>Number</u>
Internal Medicine	9/10/87	107564
Medical Oncology	11/7/89	107564

(Voluntary Recert 5/2/13)

Licensure:

<u>State</u>	<u>Date</u>	<u>Perm./Temp.</u>	<u>Number</u>	<u>Renewal Date</u>
Virginia	2/23/15	Perm	0101257805	5/31/26

VI. Professional Affiliations (including offices held)

<u>Year</u>	<u>Organization</u>
1983-	American College of Physicians (Fellow 1992)
1989-	Member, American Society of Clinical Oncology
1990-1999	Member, American Federation for Medical Research
1991-2015	Eastern Cooperative Oncology Group- GU Core Committee
1991-	Affiliate Member, Society of Urologic Oncology
1993-	Affiliate Member, American Urologic Association
1996-2014	Eastern Cooperative Oncology Group- Bladder Committee- Chair
1997-00	Chair- Membership Committee, American Society of Clinical Oncology
1998-99	Associate Medical Director Iowa City Hospice
2000-03	Member Cancer Education Committee, American Society of Clinical Oncology
2003-04	Membership Committee, American Society of Clinical Oncology
2004-06	Member ASCO Scientific Program Committee
2007-08	Chairman, Steering Committee ASCO 2008 GU Cancer Symposium
2008-09	Member, Steering Committee ASCO 2009 GU Cancer Symposium
2007-10	Member, ASCO Ethics Committee
2010-	Fellow of the American Society of Clinical Oncology
2010-11	Co-Chair Bladder Cancer Task Force, NCI Genitourinary Steering Committee
2010-13	Member ASCO's Continuing Medical Education Subcommittee
2010-2016	Member ABIM Medical Oncology Exam Committee
2011-2017	Co-Chair NCI Genitourinary Steering Committee
2013-16	Member ASCO's Scientific Program Committee
2017-	Master of the American College of Physicians
2017-2020	Member ASCO Cancer Communications Committee
2020-21	Chair Elect ASCO Cancer Communications Committee
2021-2022	Chair ASCO Cancer Communications Committee

VII. Areas of Research Interest

A. Experimental therapeutics in prostate, urothelial and renal neoplasms

Current Projects (UVA Site PI)

1. c16-170: Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)
2. A Phase 1/2 Study of REGN5678 (ANTI-PSMAXCD28) With or Without Cemiplimab (ANTI-PD-1) in Patients with Metastatic Castration-Resistant Prostate Cancer and Other Tumors Associated with PSMA Expression
3. A Phase 3, Two-part, Randomized, Open-label, Adaptive Study Comparing BMS-986365 versus Investigator's Choice of Therapy Comprising Either Docetaxel or Second Androgen Receptor Pathway Inhibitor (ARPI), in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) – recharge
4. A First-in-human, Phase 1 Dose Escalation and Expansion Study Evaluating the Safety, Tolerability and Anti-Tumor Activity of [225Ac]Ac-FL-020, an Anti-PSMA Radioconjugate (RDC), in Patients With Metastatic Castration Resistant Prostate Cancer (mCRPC)

IX. Teaching Activities

A. Classroom, Seminar, or Teaching Laboratory:

<u>Year</u>	<u>Course Title</u>	<u>(% for which responsible)</u>
1995-99	ICM- M2 Urology Lectures	15%
1995-99	M4 Pharmacology	1 hour lecture
1996	Intervention and Clinical Trials	1 hour lecture
1997-99	Death and Dying	15%
1996-99	Clinical overview of case discussions	1 hour

B. Clinical Teaching (in ward, clinic, or operating room):

<u>Year</u>	<u>Where Teaching Occurred</u>	<u>Weeks/Year</u>	<u>Hours/Week</u>
1995-99	Oncology Consults	9	20
1995-99	Uro-Oncology	48	1-2
1995-99	4JPW	4	20
1996-99	Oncology Clinic	48	4

Clinical Teaching (in ward, clinic, or operating room (cont))

<u>Year</u>	<u>Where Teaching Occurred</u>	<u>Weeks/Year</u>	<u>Hours/Week</u>
2000-2015	G70	6	10
2015-	Oncology Clinic	52	4
2015-24	Inpatient Oncology Service	1	10

C. Conferences, Grand Rounds, Journal Clubs, Etc:

Year	Type of Activity	Weeks/Year	Hours/Week
1990-99	Run Bimonthly GU-Oncology Conference	24	2 hours/month
1999-2014	Monthly GU-Oncology Conference	12	1 hour/month
2003-2015	Weekly Patient Care Conference	48	1 hour/week
2018-2019	Bimonthly Urology Oncology Patient		
	Management Conf	24	2 hours/month
2015-	UVA Oncology Patient Management	52	3 hours/month

IX. Teaching Activities (cont)

D. Teaching Committees:

1992-99 Department of Internal Medicine Housestaff Evaluation Committee
2002-2014 Cleveland Clinic Hem/Onc Fellowship committee
2015-2018 UVA Div Hem/Onc Fellowship committee

E. Student Counseling:

1996- M2 student summer project, Sheila Gailbreth

X. Other Professional Activities (Boards, Editorships, etc)

<u>Year</u>	<u>Activity</u>
1980-1983	Member, University of Texas Health Science Center at Houston, Committee for the Protection of Human Subjects
1990-99	Founding Member, Iowa Cancer Pain Relief Initiative
1991-present	Eastern Cooperative Oncology Group- GU Core Committee
1992-	Reviewer, Journal of Clinical Oncology
1992-95	University Hospitals Ambulatory Care Subcommittee
1992-93	Department of Internal Medicine, Clinical Practice Advisory Committee
1993-99	University Hospitals Biotechnology Drug Advisory Subcommittee
1993-94	Department of Internal Medicine Clinical Practice Strategic Planning Committee
1993-94	Clinical Cancer Center Coordinating Committee
1993-99	Department of Internal Medicine Resident Recruitment Committee
1994-	Reviewer, Cancer
1995-	Reviewer, Urologic Oncology
1995-	Reviewer, Cancer Investigation
1994-95	University Hospitals Adult Patient and Family Housing Taskforce
1995-99	University of Iowa Clinical Cancer Center Executive Committee
1995-99	Department of Internal Medicine Promotions Committee
1995-99	Prostate Cancer Research Program Advisory Committee
1995-96	Chair University Hospitals Laboratory Advisory Subcommittee

X. Other Professional Activities (Boards, Editorships, etc) (cont)

<u>Year</u>	<u>Activity</u>
1996	Andersen-Hebbeln Research Professorship Search Committee
1996	Membership Committee, American Society of Clinical Oncology
1996-99	Chair University Hospitals Diagnostic Services Advisory Subcommittee
1996-99	Member University Hospital Task Force to Review Special Function Laboratories
1996-99	College of Medicine- Clinical Research Committee
1996-	Reviewer, Journal of Urology
1996-99	Head Clinical Trials Support Group-University of Iowa Cancer Center
1996-99	Cancer Center Program Leader- Clinical Oncology Program
1996-99	Head Clinical Trials Support Group-University of Iowa Cancer Center
1997-2002	Editorial Board The Prostate Journal
1997-99	University Hospitals Ethical Issues Subcommittee
1997	Department of Internal Medicine Faculty Compensation Committee
1997-99	University of Iowa Cancer Center Protocol Review Committee
1997-99	University Hospitals Ethical Issues Subcommittee
1997-99	University of Iowa Cancer Center Protocol Review Committee
1998-2000	Editorial Committee, Urologic Oncology Survey Section, Urologic Oncology
1997- 2005	Reviewer, Oncology
1998	Reviewer, AHFS Drug Information
1999-2005	Member Clinical Trials Scientific Review Committee
1999-2000	Member ASCO Program Committee- GU Oncology Section
2000-2009	Member Department of Defense Prostate Cancer Research Program Integration Panel

X. Other Professional Activities (Boards, Editorships, etc) (cont)

<u>Year</u>	<u>Activity</u>
2000	Participant, NCI Kidney/Bladder Cancers Progress Review Group Roundtable Meeting
2000-03	Member Center for Clinical Research Senior Advisory Council
2002-03	Member search committee, head Dept Biostatistics/Epidemiology
2001-02	Member DSMB Cytokine Working Group Phase III adjuvant IL-2 Study
2003	Member CCF Imaging Research Task Force
2003-09	Member Professional Advisory Committee, Cleveland Clinic Home Care Services
2002-04	Editor, Web Alert Section Current Oncology Reports
2000-2001	Reviewer, Critical Reviews in Oncology/Hematology
2002	Independent Reviewer Veterans Affairs Medical Research Service
2003-12	Member editorial advisory board, Journal of Supportive Oncology
2001-	Reviewer, Lancet Oncology
2003	Reviewer, ACP-ASIM PIER Bladder Cancer Module
2003-05	Reviewer, Clinical Prostate Cancer
2003	Reviewer, Journal of Cancer Research and Clinical Oncology
2003-	Reviewer, Urology
2004-	Chair DSMB Board NIH Sponsored Phase III Trial of Energy healing and prostate cancer
2004-05	Chair Department of Defense Prostate Cancer Research Program Integration Panel
2005-10	Editorial Board, Journal of Clinical Oncology
2005-	Reviewer, European Urology
2005-	Reviewer, Clinical Cancer Research
2005	Reviewer, CA A Cancer Journal for Clinicians
2005	Reviewer, BJU

X. Other Professional Activities (Boards, Editorships, etc) (cont)

<u>Year</u>	<u>Activity</u>
2006-07	Chairman DSMB ASCENT II (Phase III Docetaxel +/-Calcitriol)-Novacea
2006-2023	Editorial Board Clinical Genitourinary Cancer
2006	Reviewer, Indian Journal of Urology
2006-	Associate Editor NEJM Journal Watch Oncology and Hematology
2006	Member search committee, Chair, Head and Neck Institute
2007	Reviewer, Journal of the National Cancer Institute
2007	Ad Hoc Reviewer NCI-Special Emphasis Panel
2007	Member search committee, Chair Dept of Molecular Genetics
2007-08	Reviewer, Annals of Oncology
2007-2010	Chairman, DSMB EFC6546 / VENICE Phase III docetaxel/with/without VEGF Trap)
2007-2016	Associate Editor for Medical Oncology, Urology, The Gold Journal
2007-2010	Member DSMB Sanofi Aventis CILAB Phase III trial, bladder cancer
2008	Reviewer, NIH-NCI Subcommittee H
2008-2010	CCF Internet Physican Advisory Council
2008-11	NCI Genitourinary Steering Committee (GUSC) Alternate member
2008-2014	Member CCLCM Committee on Appointments and Promotions
2009	Chair, Search Committee, Chair Dept of Surgical Soft Tissue Oncology
2009-10	Member, Scientific Advisory Board, Transgene, Strasbourg, France
2009-2018	Member, Management Committee, Bladder Cancer Advocacy Network
2009-11	Member, DSMB Medivation, MDV3100 Phase III Prostate Study
2009-	Reviewer, Lancet Oncology
2010-	Member, Editorial Board, Current Urology Reports

X. Other Professional Activities (Boards, Editorships, etc) (cont)

<u>Year</u>	<u>Activity</u>
2010-2012	Member Tengion Phase I DSMB
2011-2014	Member DSMB Sanofi Aventis Cabazitaxel Phase III Prostate Cancer trials
2011-12	CCF End of Life Care Steering Committee
2011-2014	Chair IDMC Dendreon Phase III N10-1
2011-2014	Member, DSMB Medivation, PREVAIL Phase III Prostate Study
2011-2019	Member Scientific Advisory Board, Bladder Cancer Advocacy Network
2012-	Editorial Board, Clinical Genitourinary Cancer
2012-2014	Case Western GI Spore Internal Advisory Board
2013-2015	Member DSMB Medivation TERRAIN study
2013-2017	Editorial Board Oncology & Biotech News
2015	Member NCRI Bladder Cancer Clinical Studies Group, Progress Review (MRC London)
2015	Member Review Team Site Visit, NCI GU Oncology Branch
2015-18	Member AUA Muscle Invasive Bladder Cancer Panel
2017	Scientist Reviewer for the DOD Prostate Cancer Research Program FY17 Clinical Consortium Award
2018-2020	Member, Lancet Oncology International Advisory Board
2018-2020	Member ASCO-SITC Immuno-Oncology Symposium Program Committee
2018	Chair DOD Clinical & Experimental Therapeutics-2 (CET-2) peer review panel
2018-21	Member AUA Advanced Prostate Cancer Guidelines Panel
2019	Peer Reviewer AUA Diagnosis and Treatment of Early Stage Testicular Cancer Guideline
2020-	Chair DSMB Phase 1/2 Study of Modern Immunotherapy in BCG-Relapsing Urothelial Carcinoma of the BLADDER – (ADAPT-BLADDER) HCRN GU16-243

X. Other Professional Activities (Boards, Editorships, etc) (cont)

<u>Year</u>	<u>Activity</u>
2020-25	ABIM's Medical Oncology Longitudinal Assessment Approval Committee
2020	Member IDMC Merck MK6482-011, MK6482-012, MK6482-005
2020	Chair DOD Prostate Cancer (PCRP), Idea Award, Clinical Experimental Therapeutic Panel
2020	Scientific Committee member for 1st ECO Cancer Immunotherapy Breakthrough Meeting (Madrid, Spain)
2021-	Reviewer NEJM
2021	Chair- ASCO Conquer Cancer Advanced Clinical Research Award Review Committee
2022-	Member External Advisory Board Atrium Health Wake Forest Baptist Comprehensive Cancer Center
2022	Member MACRA Episode-Based Cost Measure Wave 5 Clinician Expert Prostate Cancer Workgroup

XI. Clinical Activities

- A. Inpatient:
 - 1. 1 week/year Solid Tumor inpatient Service
- B. Outpatient
 - 1. 3 half day Oncology Clinics/week

XII. Honors and Awards

<u>Year</u>	<u>Honor</u>
1992	Fellow of the American College of Physicians
2003	Cleveland Clinic Teacher of the year Dept Hematology/Oncology
2010	Fellow of American Society of Clinical Oncology
2013	Cleveland Clinic Solid Tumor teacher of the year
2016	Master of the American College of Physicians
2018	NCI Director Service Award

XIII. Financial Resources (Grants and Contracts)

A. Federal

5P30CA044579-27 Loughran (PI), Dreicer (Co-I) 09/16/1997-01/31/2022

NIH/NCI

Cancer Center Support Grant – Deputy Director and Associate Director for Clinical Research

This grant supports the basic science and clinical research programs at the University of Virginia Cancer Center.

1R01NR016483-01A1 (Jones-PI, Dreicer Co-I) 02/06/2017-12/31/2021

NIH

Decision Navigation for Advanced Prostate Cancer Treatment Options using mHealth

The study's primary aim is to test the effects of a theory-based mHealth DA (CHAMPION) administered by Registered Nurse (RN)-Community Patient Navigator (CPN) teams to advanced prostate cancer patients and decision partners/proxies on the following outcomes: less decisional conflict/uncertainty, higher psychosocial quality of life domain (HRQL-PSY), and less regret at the time of making an anti-cancer treatment decision

PSAUVAGW00 Dreicer (PI) 02/01/2012-01/31/2022

NCI

Frontier Science and Technology Research Foundation Contract #PSAUVAGW00

UVA will enter eligible patients onto the Eastern Cooperative Oncology Group (ECOG) clinical trial protocols and will furnish timely data, specimens and follow up information to the ECOG Coordinating Center as outlined in the protocols.

XIV. Physical Facilities

P.O. Box 800716 6261 Multi-Story Building Charlottesville, VA 22908-0716

XV. Personnel Currently Supervised

Faculty in Section of Medical Oncology, Jennifer Eccles, PA, GU research personnel

IVI Papers Published or In Press

1. **Dreicer, R...**, and Alexanian, R.: Nonsecretory Multiple Myeloma. *Am J. Hematol.* 13:311, 1982.
2. Alexanian, R., and **Dreicer, R...**: Chemotherapy for Multiple Myeloma. *Cancer.* 53:513, 1984.
3. Kantarjian, H., Dreicer, R., Barlogie, B., Plunkett, W., and Alexanian, R.: High-dose Cytosine Arabinoside in Multiple Myeloma. *Eur. J. Cancer Clin. Oncol.* 20:227, 1984.
4. Falkson, G., Gelman, R.C., **Dreicer, R...**, Alberts, A.S., Coccia-Portugal, M.A., Tormey, D.C., Bennet, J.M., and Carbone, P.P.: Myelodysplastic Syndrome and Acute Non-Lymphoblastic Leukemia Secondary to Treatment with Dibromoducitol Developing In Patients With Breast Cancer. *J. Clin. Oncol.*, 7:1252, 1989.
5. Schiller, J.H., Storer, B., **Dreicer, R...**, Rosenquist, D., Frontiera, M., and Carbone, P.P.: A Randomized Phase II/III Trial of Combination Beta and Gamma Interferons Etoposide and Cisplatin in Inoperable Non-Small Cell Cancer of the Lung. *J. Natl. Cancer Inst.*, 81:1739, 1989.
6. **Dreicer, R...**, Messing, E.M., Loehrer, P.J., and Trump, D.L.: Perioperative Methotrexate, Vinblastine, Doxorubicin and Cisplatin (M-VAC) for Poor Risk Transitional Cell Carcinoma of the Bladder: An Eastern Cooperative Oncology Group Pilot Study. *J Urol.*, 144:11123, 1990.
7. **Dreicer, R...**, See, W.A., and Williams, R.D.: Current Controversies in Urologic Oncology. *Iowa Med.*, 81:343 1991.
8. **Dreicer, R...**, and Wilding, G.: Steroid Hormone Agonists and Antagonists in the Treatment of Cancer. *Cancer Invest.*, 10:27, 1992.
9. **Dreicer, R...**, and Love, R.R.: High Total Dose 5-Fluorouracil Treatment During Pregnancy. *Wis. Med. J.*, 90:582, 1991
10. **Dreicer, R...**, Donovan, J., Benda, J.A., Lund, J., and DeGowin, R.L.: Erythrocytosis in a Young Adult with an Erythropoietin Producing Wilms' Tumor. *Am. J. Med.*, 93:229, 1992.
11. **Dreicer, R...**: Pain and Symptom Management in Hormone-Refractory Prostate Cancer. *Reviews on Endocrine-Related Cancer.*, 40:13, 1992
12. **Dreicer, R...**, Kollmorgen, T., Smith, R., and Williams, R.D.: Neoadjuvant Cisplatin, Methotrexate, Vinblastine (CMV) for Muscle Invasive Bladder Cancer. *J. Urol.*, 150:849, 1993.
13. **Dreicer, R...**, and Gesme, D.H., Jr.: Cancer Pain Management: Inadequate. *Iowa Medicine*, 84:252, 1994
14. Loehrer, P.J., Elson, P., **Dreicer, R...**, Hahn R., Nichols, C.R., Williams, R.D., Einhorn, L.E.: Escalated Dosages of Methotrexate, Vinblastine, Doxorubicin and Cisplatin Plus rhG-CSF in Advanced Urothelial Carcinoma: An ECOG Trial. *J. Clin Oncol.*, 12:483, 1994.
15. Sandlow, J., Cohen, M.B., Robinson, R.A., **Dreicer, R...**, and Williams, R.D.: DNA Ploidy and P glycoprotein Expression as Predictive Factors of Response to Neoadjuvant Chemotherapy for Invasive Bladder Cancer. *Urology*, 43:787, 1994.

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16. **Dreicer, R...**, Forest, P.K., and Williams, R.D.: Phase II Trial of 5-Fluorouracil and Alpha 2B in Patients with Hormone-Refractory Metastatic Prostate Cancer. *Urology*, 44:377, 1994.
17. Kahn, D., Williams, R.D., Libertino, J., Hirschorn, M., Seldin, D., **Dreicer, R...**, Bushnell, D., and Gulfo, J.: Radioimmunosciintigraphy with In111-labeled CYT-356 for the Detection of Occult Prostate Cancer Recurrence. *J. Urol.*, 152:1490, 1994.
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19. Einhorn, L.H., Roth, B.J., Ansari, R., **Dreicer, R...**, Loehrer, P.J.: Vinblastine, Ifosfamide and Gallium (VIG) Combination Chemotherapy in Urothelial Carcinoma. *J. Clin. Oncol.*, 12:2271, 1994.
20. **Dreicer, R...**, Cooper, C., and Williams, R.D.: The Management of Prostate and Bladder Cancer in the Elderly. *Urol. Clin. N. America*, 23:87, 1996.
21. See, W.A., Laurento, J., **Dreicer, R...**, and Hoffman, H.: Testicular Carcinoma Metastatic to the Neck. *J. Urol.*, 155:590, 1996.
22. See, W.A., **Dreicer, R...**, Wheeler, J.A., Forest, P.K., and Loening, S.: Brachytherapy and Continuous infusion 5-Fluorouracil for the Treatment of Locally Advanced, Node Negative Prostate Cancer: A Phase I Trial. *Cancer.*, 77:924, 1996.
23. Clamon, G., Riggs, C., **Dreicer, R...**, and Hohl, R.: Phase II Trial of Edatrexate in Patients with Metastatic Colorectal Cancer. *Invest. New Drugs.* 13:359, 1996.
24. Dreicer R., Gustin, D.M., See, W.A., and Williams, R.D.: Paclitaxel in Advanced Urothelial Carcinoma: Its Role in Patients with Renal Insufficiency and as Salvage Therapy. *J. Urol*, 156:1606, 1996.
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26. **Dreicer, R...**, Kemp, J., Stegink, L., Cardillo, T., Forest, P., See, W.A: A Phase II Study of Deferoxamine in Patients with Hormone-Refractory Prostate Cancer. *Cancer Investigation.*, 15:311, 1997.
27. **Dreicer, R...**, Propert, K.J., Kuzel, T., Kirkwood, J.M., O'Dwyer, P.J., and Loehrer, P.J.: A Phase II Trial of Edatrexate in Patients with Advanced Renal Cell Carcinoma. An Eastern Cooperative Oncology Group Study. *Am. J. Clin. Oncol.*, 20: 251, 1997.
28. Dreicer R.: Metastatic Prostate Cancer: Assessment of Response to Systemic Therapy. *Sem.Urol. Oncol.*, 15:28, 1997.
29. **Dreicer, R...**, Propert, K.J. , Roth, B., Einhorn LH., and Loehrer, P.: Vinblastine, Ifosfamide and Gallium Nitrate in Advanced Urothelial Carcinoma: An Eastern Cooperative Oncology Group Phase II Study. *Cancer*, 79:110, 1997.

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30. Witte, R.S., Elson, P., Bono, B., Knop, R., Haberman, T., **Dreicer, R...**, and Loehrer, P.J.: An ECOG Phase II Trial of Ifosfamide in the Treatment of Previously Treated Advanced Urothelial Carcinoma. *J. Clin. Oncol.*, 15:589, 1997.
31. See, W.A., **Dreicer, R...**, Forest, P.K., and Riggs, CE.: Continuous Infusion Intravesical Doxorubicin for the Treatment of Regionally Advanced Bladder Cancer. *Am. J. Clin. Oncol.*, 20:331, 1997.
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44. **Dreicer, R...**: Locally Advanced and Metastatic Bladder Cancer. *Current Treatment Options in Oncology* 2:431, 2001
45. Klein, E.A., Kupelian, P.A., **Dreicer, R...**, Peereboom, D., Zippe, C: Locally Advanced Prostate Cancer. *Current Treatment Options in Oncology* 2:404, 2001

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46. Mahmoud-Ahmed, A.S., Suh, J.H., Kupelian, P.A., Klein, E.A., Peereboom, D.M., **Dreicer, R...**, Barnett, G.H.: Brain Metastases From Urinary Bladder Carcinoma: Presentation, Treatment, And Survival. *J Urol* 167:2419, 2002
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XVII Books and/or Chapters, Abstracts, Editorials, Letters

A.Books and/or Chapters

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80. Rosenberg, J.E., Ballman, K.V., Halabi,S., Watt, C., Hahn, O.M., Steen, P.D., **Dreicer,R.**, Flaig, T.W., Stadler, W.M., Sweeney, C., Mortazavi, A., Morris, M.J. CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma. J Clin Oncol 37, 2019 (suppl; abstr 4503
81. Agarwal, N., Loriot, Y., McGregor, B.A., **Dreicer, R.**, Dorff, T.B., Maughan, B.L., Kelly, W.K., Pagliaro, L.C, Srinivas, S., Squillante, C.M., aishampayan, U.N., Wang, E.W, Curran, D., Choueiri, T.K., Pal, S.K.. Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results of cohort 6 of the COSMIC-021 study.J Clin Oncol 38: 2020 (suppl; abstr 5564)

E. Presentations:

1. "Recent Developments in the Treatment of Metastatic Prostate Cancer." Progress in Internal Medicine Conference, University of Iowa, September, 1989
2. Therapy of Advanced Renal Cancer." Texas Association of Genitourinary Surgeons Meeting, Iowa City, 1990.
3. "Pain Management in the Patient with Cancer." Des Moines VA, October, 1990.
4. Pain Management in the Cancer Patient." Iowa Urologic Society Meeting, Iowa City, IA, September 15, 1990.
5. "Recent Developments in Prostate Cancer Management." Departmental Grand Rounds, December 20, 1990.
6. "Pain Management in the Patient with Cancer." Tumor Board, Sterling, Illinois, March 20, 1991.
7. "Prostate Cancer in the Elderly." Geriatric Education Fellowship Program, Iowa City, IA April 8, 1991.
8. Postgraduate Course on Chemotherapy of Urologic Cancers, American Urologic Association Meeting, Toronto, Canada, June, 1991. (1) "Chemotherapy of Testicular Cancer"; (2) " Hematopoietic Growth Factors"; (3) " Pain Management in Uro-Oncology"; (4) " Chemotherapy- Principles and Practices".
9. "CMV Chemotherapy for Muscle-Invasive and Metastatic Bladder Cancer: Long-term Follow-up." American Urologic Association Meeting, Washington, DC, May, 1992.
10. "Hypercalcemia of Malignancy". Grand Rounds, St. Vincent's Hospital, Indianapolis, IN May, 1992.
11. "Cancer Pain Management." VA Medical Center, Des Moines, IA, August, 1992.
12. "Treatment Options in Stage D3 Prostate Cancer." Iowa Urologic Society Meeting, Iowa City, IA September 19, 1992. Urology Postgraduate Conference
13. "New Approaches to the Management of Advanced Breast Cancer." Mercy Hospital Tumor Board, Cedar Rapids, IA December 7, 1992.
14. "Cancer Pain Management" Surgery Rounds, Des Moines VA, March 26, 1993.
15. "Use and Misuse of PSA." Iowa Medical Society, 1993 Scientific Session, Des Moines, IA, April 15, 1993.
16. "Experimental Therapeutics in Prostate Cancer." Urology Postgraduate Conference/Iowa Urologic Society Meeting, Iowa City, IA September 18, 1993.
17. "The Role of Finasteride in the Management of BPH." Iowa City Medicine Lecture, Mercy Hospital, October 13, 1993.
18. Medical Management of Cancer Pain in the Older Patient." ACS Conference-Management of Cancer Pain in the Elderly, Ankeny, IA, October 23, 1993.
19. "The Role of Opioids in the Management of Pain." Quarterly Staff Meeting, St. Elizabeth Hospital, Lincoln, NE, October 27, 1993.
20. "Cancer Pain Management." Grand Rounds, VA Hospital, Lincoln, NE October 27, 1993.
21. "PSA and Prostate Cancer Screening: A Reappraisal." Cedar Rapids, IA, March 11, 1994.
22. "The Importance of Cancer Pain Initiatives." Fourth Annual Conference for Pharmacists and Nurses, Omaha, NE, April 9, 1994.

Presentations (cont):

23. "Neoadjuvant and Adjuvant Chemotherapy in Advanced Bladder Cancer" "Management of Metastatic Bladder Cancer" Postgraduate Course on Bladder Cancer, American Urologic Association Meeting, San Francisco, CA, May 1994.
24. "Assessment and Management of the Patient in Pain." Immanuel Hospital, Omaha, NE June 1994.
25. "Cancer Pain Management" St. Joseph Hospital, Creighton University, June 1994.
26. "Prostate Cancer Screening" Grand Rounds, Department of Internal Medicine, Iowa City, IA, June 1994.
27. "Cancer Pain Management" Staff Conference, Department of Medicine, Des Moines VA, Des Moines, IA, September 16, 1994.
28. "The Management of Cancer Pain" Internal Medicine Grand Rounds, University of South Dakota School of Medicine, September 28, 1994.
29. "The Management of Chemotherapy Induced Nausea and Vomiting", "Cancer Pain Management"; "Prostate Cancer Screening: A Cautious Approach" Fall Cancer Update, Mason City, IA, October 13, 1994.
30. "Salvage Chemotherapy for Resistant Testis Cancer" Charite' Testis Cancer Symposium, Berlin, Germany, October 29, 1994.
31. "Medical Management of Cancer Pain in the Elderly" 2nd Annual Pain Management Seminar, Mercy Hospital, Des Moines, IA November 19, 1994.
32. "Current Research on the Management of Hormone Refractory Prostate Cancer" 2nd Uniformed Services Urology Research Group Seminar, Denver, CO December 10, 1994.
33. "Prostate Cancer Screening" Family Practice Refresher Course, Iowa City, IA, March 8, 1995.
34. "Neoadjuvant and Adjuvant Chemotherapy in Advanced Bladder Cancer", "Management of Advanced Bladder Cancer" Postgraduate Course on Bladder Cancer, American Urologic Association Meeting, Las Vegas, NV, May 1995.
35. "Oncologic Evaluation of the Patient with Melanoma", "Recent Advances in the Treatment of Metastatic Melanoma" Diagnosis and Management of Choroidal Melanoma, Iowa City, IA July 15, 1995.
36. "Palliative Care Pathways" Psychological Oncology Conference, Holiday Inn, Iowa City,
37. "Pain is Still With Us" Staff Conference, St. Mary's Medical Center, Evansville, IN, September 13, 1995.
38. "Cancer Pain Management: A Quantum Leap for the Year 2000" Staff Rounds, Fairview Southdale Hospital, Minneapolis, MN, September 21, 1995.
39. "Cancer Pain Management" Iowa Hospice Annual Conference, Des Moines, IA September 22, 1995.
40. "The Management of Prostate Cancer in the Elderly" Midwestern Conference on Health Care in the Elderly, Iowa City, IA September 30, 1995.
41. "Cancer Pain Management" Iowa Physician Assistant Society Meeting, Iowa City, IA 10/5/95

Presentations (cont):

42. "The Management of Advanced Bladder Cancer: Progress and Potential" Cancer Center Grand Rounds, University of Wisconsin Clinical Cancer Center, Madison, WI, October 25, 1995.
43. "Phase II Trial of Vinblastine, Ifosfamide and Gallium Nitrate in Platinum and Taxol Resistant Ovarian Cancer" Amgen Clinical Investigator Symposium, Thousand Oaks, CA, January 12, 1996.
44. "Recent Developments in Cancer Pain Management" Tumor Board, Mercy Medical Center, Cedar Rapids, IA, March 11, 1996.
45. "Paclitaxel in Advanced Urothelial Carcinoma" American Urological Association Meeting, Orlando, FL May 8, 1996
46. "Cancer Pain Management" Genesis Medical Center, Davenport, IA June 4, 1996.
47. "Cancer Pain Management" Cedar Valley Hospice, Waterloo, IA June 6, 1996.
48. "The Management of Pain in Patients with Advanced Disease", Staff Conference, John MO, Moline, IL 8/8/96.
49. "Controversies in Breast Cancer" Mercy Medical Center Cancer Update, Cedar Rapids, IA 9/5/96.
50. "The Management of Advanced Bladder Cancer" Iowa Urologic Society Annual Meeting, Iowa City, IA 9/6/96.
51. "Cancer Pain Management" South Dakota State Pain Initiative Annual Conference, Sioux Falls, SD 9/14/96
52. "The Management of Advanced Bladder Cancer-Beyond M-VAC" Eastern Cooperative Oncology Group, Education Seminar, Miami, FL 10/2/96.
53. "Cancer Pain Management" Medicine Grand Rounds, Michigan State University, Kalamazoo Center for Medical Studies. Kalamazoo, MI 10/16/96
54. "The Management of Advanced Bladder Cancer-Beyond M-VAC" Uro-Oncology Update for Urologists and Oncologists, New Orleans, LA, 11/22/96.
55. "The Role of Opiates in the Management of Malignant and Non-Malignant Pain" Illinois Association of Osteopathic Physicians and Surgeons, Schaumburg, IL 12/8/96.
56. "Prostate Cancer Management: Clinical Realities and Challenges" Internal Medicine Grand Rounds, University of Iowa, 1/9/97.
57. "Cancer Pain Management" Grinnell Regional Hospital, Grinnell, Iowa, 2/20/97.
58. "The Role of Opiates in the Management of Cancer and Non-Malignant Pain" Management of Chronic Disease Symposium- Southern Illinois University, Dekatur, Illinois, 2/28/97.
59. "Cancer Pain Management" Wapello County Medical Society, Ottumwa, IA, 3/4/97.
60. "Adjuvant Chemotherapy for Bladder Cancer" Society of Urologic Oncology, New Orleans, LA 4/12/97
61. "Cancer Pain Management", and "The Role of Palliative Care in Patients with Malignancy" Hospice of Central Iowa, Des Moines, IA 5/10/97
62. "The Management of Cancer Pain" Midlands Hospital, Omaha, NE 5/12/97.
63. "Cancer Pain Management" Huron Regional Medical Center, Huron, SD 9/18/97
64. "Cancer Pain Management" Jasper County Medical Society, Newton, IA 10/9/97.
65. "The Management of Malignant and Nonmalignant Pain", Illinois Academy of Family Physicians, Saint Francis Medical Center, Peoria IL. 10/23/97

Presentations (cont):

66. "Pain and Symptom Management of Patients with End-Stage Disease Progress in Internal Medicine, Iowa City, IA 10/23/97
67. "The Management of Malignant and Nonmalignant Pain"- Medicine Grand Rounds Southern Illinois University, Springfield, IL 3/10/98
68. "The Management of Advanced Bladder Cancer: Old Challenges, New Opportunities" Cancer Center Grand Rounds, University of Wisconsin, Clinical Cancer Center. Madison, WI, 3/25/98.
69. "The Management of Malignant and Nonmalignant Pain", Illinois Academy of Family Physicians, Springfield, IL. 4/9/98
70. "End of Life Care" Iowa Medical Society Annual Meeting, Des Moines, IA 4/17/98
71. "New Agents in Advanced Bladder Cancer" American Society of Clinical Oncology, Educational Session, Annual Meeting, Los Angeles, CA 5/16/98
72. "The Management of Advanced Bladder Cancer: Old Challenges, New Opportunities" University of Rochester, Rochester, N.Y. 7/30/98
73. "The Management of Advanced Bladder Cancer" Twin Cities Oncology Group, Minneapolis, MN 8/9/98
74. "New Agents In Advanced Bladder Cancer" , "Response Assessment in Bladder Preservation" National Urologic Oncology Update, Cleveland, OH 8/29/98
75. "Management of Hormone-Refractory Prostate Cancer" Oncology Update for Primary Care Algent Health Care Center, Omaha NE 9/11/98
76. "Management of Advanced Bladder and Renal Cell Carcinoma" Vanderbilt University, Nashville, TN 9/18/98
77. "The Management of Advanced Bladder Cancer: Old Challenges, New Opportunities" The Arizona Clinical Oncology Society, Scottsdale, AZ 10/24/98
78. "End of Life Care" Mercy Medical Center, Cedar Rapids, IA 4/27/99
79. "Cancer Pain Management" Iowa Palliative Care Conference, Coralville, IA 4/30/99
80. "The Management of Advanced Bladder Cancer-Beyond M-VAC" University of Illinois, Chicago, Chicago, IL 10/7/99
81. "Evidence Based Management of Bladder Cancer" Virginia Commonwealth University Third Annual Cancer Symposium, Richmond, VA 10/9/99
82. "Prostate Cancer Management for The Internist" Methodist Hospital Grand Rounds, Des Moines, IA 10/22/99
83. "The Management of Malignant and Nonmalignant Pain" Des Moines General Hospital 10/22/99
84. "The Management of Advanced Bladder Cancer", "Neoadjuvant and adjuvant therapy for bladder cancer", National Urologic Update, Brooklyn, N.Y. 11/5/99
85. "Beyond M-VAC Contemporary Management of Advanced Bladder Cancer" University of California San Diego- VA Hospital. San Diego, CA 4/6/00
86. "The Role of Opioids in the Management of Cancer Pain" Urology Grand Rounds The Medical College of Wisconsin. Milwaukee, WI 5/5/00
87. "Genitourinary Cancer" ASCO 2000 Review" Methodist Hospital, Omaha, NE 6/10/00
88. "Prostate Cancer Management: An Update for Oncologists" Ohio-West Virginia Oncology Society, Annual Meeting, Sandusky, OH 9/9/00

Presentations (cont):

89. "Clinical Research In Advanced Prostate Cancer: Challenges and Opportunities" Cancer Center Grand Rounds, University of Iowa, Iowa City, IA 9/13/00
90. "Neoadjuvant Therapy for Prostate Cancer" Aventis Prostate Investigators Meeting, Lake Tahoe, NV 9/19/00
91. "Neoadjuvant and Adjuvant Therapy for Bladder Cancer" National Urologic Oncology Update, Chicago, IL 10/20/00
92. "Clinical Research In Advanced Prostate Cancer: Challenges and Opportunities" Case Western University, Cleveland, OH 11/10/00
93. "Recent Advances in Prostate Cancer Management" Wisconsin Cancer Center Waukesha, WI 4/11/01
94. "Genitourinary Oncology ASCO 2001 Review", Good Samaritan Hospital Dayton, OH 5/30/01
95. "Androgen Independent Metastatic Prostate Cancer", Mercy Hospital, Pittsburgh, PA 9/10/01
96. "Cancer Pain Management" Mountain States Tumor Board, Boise, ID 10/12/01
97. "The Management of Androgen Independent Metastatic Prostate Cancer", National Urologic Oncology Update, San Francisco CA, 11/9/01
98. "Management of Prostate Cancer with Biochemical Failure" Multidisciplinary Genitourinary Oncology Conference, Cleveland, OH 11/13/01
99. "GM-CSF + Thalidomide in Prostate Cancer" 5th Annual Regional Cancer Center Consortium for Biological Treatment of Cancer" Cleveland, OH 2/23/02
100. "Cancer Pain Management" St Josephs Regional Medical Center Tumor Board, South Bend, Indiana 2/27/02
101. "Management of Advanced Renal Cell Carcinoma" West Virginia University-Charleston, WV 4/29/02
102. "Management of Locally Advanced Bladder Cancer" Meet The Professor Session American Society of Clinical Oncology Meeting, Orlando, FL 5/18, 5/20/02
103. "Practical Management of the Rising PSA Syndrome" Education Session, American Society of Clinical Oncology Meeting, Orlando, FL 5/19, 5/20/02
104. "Management of Advanced Renal Cell Carcinoma" Howard University Cancer Center, Washington D.C., 5/23/02
105. "Prostate and Testicular Cancers" Cleveland Clinic Internal Medicine Board Review Cleveland, OH 6/14/02
106. "Beyond M-VAC Contemporary Management of Advanced Bladder Cancer" University of Cincinnati, Hematology/Oncology Grand Rounds, Cincinnati, OH 9/13/02
107. "Management of Locally Advanced Prostate Cancer" ; "The Management of Androgen Independent Metastatic Prostate Cancer" , Fellows conference, Hem/Onc Staff Dinner Mayo Clinic Jacksonville, Jacksonville, FL 9/18/02
108. "Management of Androgen Independent Metastatic Prostate Cancer" AUA Southeast Section Meeting, Colorado Springs, CO 10/7/02
109. "Beyond M-VAC Contemporary Management of Advanced Bladder Cancer" Bethesda Hospital, Zanesville, OH 10/17/02
110. "Management of Advanced Renal Cell Carcinoma" Hematology/Oncology Grand rounds University of Maryland Cancer Center, Baltimore MD, 11/11/02

Presentations (cont):

111. "Management of Prostate Cancer With Evidence of Biochemical Failure"
Multidisciplinary Genitourinary Cancer, Cleveland, OH 11/19/02
112. "Management of Advanced Renal Cell Carcinoma" Hematology/Oncology Grand Rounds
Lennox Hill Hospital, NY 12/03/02
113. "Prostate Cancer: Issues and Controversies for the Internist" Div of Medicine Grand
Rounds, Cleveland Clinic Foundation, Cleveland, OH 12/5/02
114. "Role of Nephrectomy in Metastatic Renal Cancer Con" Society of Urologic Oncology NCI
Joint Conference, Bethesda MD 12/13/02
115. "Evolving Concepts in the Management of Prostate Cancer" Miami Baptist Hospital
Miami, FL 2/6/03
116. "The evolving role of chemotherapy in the management of prostate cancer" Challenging
Cases In Urology, Miami, FL 2/7/03
117. "Rising PSA Can you afford to wait" Scripps Annual Hematology/Oncology Review La
Jolla CA, 2/17/03
118. "Evolving role of chemotherapy in prostate cancer" NOCR annual meeting Las Vegas, NV
2/21/03
119. "Role of Chemotherapy in Advanced Prostate Cancer" Wilford Hall Airforce Base, San
Antonio, TX 3/26/03
120. "Developments in the management of Advanced renal cell carcinoma" Cancer Center
Grand Rounds, University of Rochester, Rochester, NY, 4/20/03
121. "Evolving role of chemotherapy in advanced prostate cancer" Hem/Onc divisional
conference, Stanford University, Palo Alto, CA, 4/21/03
122. "Developments in the management of Advanced renal cell carcinoma" State University
of NY Downstate, Brooklyn, NY 5/23/03
123. "The Management of Rising PSA Syndrome" Meet the professor session American Society
of Clinical Oncology, Chicago, IL 5/31/03
124. "Phase III Trial of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC)
Versus Carboplatin and Paclitaxel in Patients with Advanced Carcinoma of the
Urothelium: A Trial of the Eastern Cooperative Oncology Group" GU Oral Session
American Society of Clinical Oncology, Chicago, IL 6/1/03
125. "The Evolving role of Systemic Therapy in the Management of Prostate Cancer" Mayo
Clinic Hematology/Oncology Review, Amelia Island, FL 8/9/03
126. "The Evolving Paradigm in Prostate Cancer Clinical Research" Baylor College of
Medicine, Houston, TX 8/12/03
127. "Integration of a multidisciplinary approach to the management of the prostate cancer
patient" New Paradigms in the Management of Prostate Cancer" Loyola University,
Chicago IL, 10/4/03
128. "The Evolving Paradigm in Prostate Cancer Clinical Research" VICCAN fall research
conference, Vanderbilt Ingram Cancer Center, Nashville, TN 10/25/03
129. "The Evolving Paradigm in Prostate Cancer Clinical Research" Cancer Center Grand
Rounds, Roswell Park, Buffalo, NY 10/31/03
130. "The Evolving Paradigm in Renal Cell Carcinoma Clinical Research" Cancer Center
Grand Rounds, University of Wisconsin, Madison 12/3/03

Presentations (cont):

131. "The Management of Androgen Independent Prostate Cancer. Hem/Onc grand rounds
Metro Health Center, Cleveland, OH 1/8/04
132. "14th Annual International Challenging Cases in Urology- Renal, Prostate, Bladder"
Invited panelist, Miami, FL 2/20/04
133. "Debate with the Experts: Contemporary Prostate Cancer Treatments. Univ Pittsburgh
Pittsburgh, PA 3/12/04 Invited panelist
134. "Evolving strategies in the management of chemotherapy induced nausea and vomiting"
Medicine Grand Rounds, East Orange VA Medical Center, Newark NJ, 3/24/04
135. "Advances in the management of androgen-independent prostate cancer" Advances In
Urology, San Diego, CA 3/27/04
136. "The Evolving Paradigm in Prostate Cancer Clinical Research" Karmonas Cancer
Center Grand Rounds, Detroit, MI 4/15/04
137. "The Evolving role of Chemotherapy in the Management of Prostate Cancer"
Allegheny General Hospital, Pittsburgh, PA 5/13/04
138. "The Evolving role of Chemotherapy in the Management of Prostate Cancer"
Genitourinary Malignancies Conference, Univ of Iowa, Iowa City, IA 6/25/04
139. "The Evolving role of Chemotherapy in the Management of Prostate Cancer"
Fairview Hospital Tumor Board, Lakewood, OH 7/9/04
140. "The Evolving role of Chemotherapy in the Management of Prostate Cancer"
Gwinnett Hospital System, Tumor Board, Atlanta, GA 8/12/04
141. "Evolving Management of Androgen Independent Prostate Cancer" Moffitt Cancer Center
Prostate Cancer Research Symposium, Orlando FL 10/8/04
142. "Management of Androgen Independent Prostate Cancer" University of Minnesota
Fairview Hospital. 10/22/04 Minneapolis, MN
143. "Advances in the Management of Advanced Prostate Cancer" Prostate Cancer Conference
University of Cincinnati, Cincinnati OH, 11/6/04
144. "Evolving role of Chemotherapy in Advanced Prostate Cancer" Presbyterian Hospital,
Tumor Board, Charlotte, NC 11/10/04
145. "Advances in the Management of Advanced Prostate Cancer" Ohio Urologic, Ohio Mid
Central CCOP meeting, Columbus, OH 11/11/04
146. "Revlimid in Advanced Renal Cell Carcinoma" Kidney Cancer Association National
Meeting, Chicago, IL 11/14/04
147. "Management of Androgen Independent Prostate Cancer" Hem/Onc Grand Rounds
North Shore University Medical Center, Manhasset, NY 11/16/04
148. "Neoadjuvant Chemotherapy in Prostate Cancer" Society of Urologic Oncology Meeting
Bethesda, MD 12/3/04
149. "Management of Androgen Independent Prostate Cancer" Oncology Grand Rounds
Sparrow Hospital System, Lansing Michigan 1/28/05
150. "The Evolving Paradigm of Prostate Cancer Clinical Research" Oncology Grand Rounds
Emory University, Atlanta GA 2/2/05
151. Panelist Prostate, Bladder, Kidney Cancers" "Challenging Cases in Urology" Miami, FL
2/26/05
- "Evolving role of systemic therapy in prostate cancer" Oncology Grand Rounds University of
Rochester, Strong Memorial Hospital Rochester, NY 3/7/05

Presentations (cont):

152. "Management of Atypical Urothelial Cancers" Meet The Professor Session, American Society of Clinical Oncology Meeting, Orlando, Florida 5/14/05
153. "Management of Advanced Prostate Cancer" Florida Hospital, Orlando FL 9/7/05
154. "Management of Advanced Bladder Cancer" Aultman Cancer Center Annual Update Canton, OH 9/23/05
155. "Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: State of the Art?" Society of Urologic Oncology Annual Meeting, Bethesda MD, 12/2/05
156. "What is optimal hormonal therapy for prostate cancer?" ASCO Prostate Meeting, San Francisco, CA 2/26/06
157. "Advances in GU Oncology" and "Current Status of Medical Oncology in the U.S." Japanese Society of Medical Oncology, Osaka, Japan 3/17-3/18/06
158. "Evolving Role of Systemic Therapy in Prostate Cancer", "The Management of Poor Risk Testicular Cancer: Remaining Challenges" "Paradigm Shift: New Approaches to the
159. Management of Advanced Kidney Cancer" University of Cairo, Department of Urology, Cairo Egypt, 4/1-3/06
160. "Evolving role of systemic therapy in prostate cancer" Rush University Hospital Hematology/Oncology Grand Rounds, Chicago, IL 4/20/06
161. "Prostate Cancer and Bone" Bone Innovation Summit, Cleveland, OH 5/4/06
162. "Small cell carcinoma of the bladder" Clinical Problems in Oncology American Society of Clinical Oncology Annual Meeting, Atlanta, GA 6/4/06
163. "Highlights of the Day: GU Oncology" American Society of Clinical Oncology Annual Meeting, Atlanta, GA 6/5/06
164. "ASCO Highlights" American Society of Clinical Oncology GU Oncology Reston VA 6/22/06
165. Urologic Oncology Roswell Park ASCO Review, Buffalo, NY 7/15/06
166. "Beyond M-VAC: Contemporary Management of Advanced Urothelial Cancer" Algent Health Cancer Conference, Omaha, NE 9/8/2006 XX.
167. "Recent Developments in the Management of Advanced Prostate and Kidney Cancer" Wings Cancer Conference, Memphis TN 9/15/06
168. "Bone issues in The Patient with Advanced Prostate Cancer" Chicago Supportive Care Conference, Chicago IL 9/29/06
169. "Advances in Prostate Cancer Management" NOCR Annual Meeting, Las Vegas, NV 2/17/07
170. "Management of the Patient with Advanced Bladder Cancer" Scripps Annual Hematology/Oncology Review, San Diego, CA 2/19/07
171. "The role of chemotherapy in non clear cell renal cancer" International Congress on Kidney and Bladder Cancer, Orlando, FL 8/5/07
172. "Chemotherapy as palliative therapy in Patients with Advanced Prostate Cancer" Chicago Supportive Care Conference, Chicago IL 9/28/07
173. "Role of novel agents in advanced renal cell carcinoma" Multidisciplinary GU Oncology Chicago, IL 9/29/07
- "Evolving Paradigm of Prostate Cancer Clinical Research" University Hospitals of Cleveland Hematology/Oncology Grand Rounds, Cleveland, OH 10/17/07

Presentations (cont):

174. "Novel therapeutics in GU Malignancies" Forum Health Annual Cancer Symposium
Youngstown, OH 12/13/07
175. "Locally Advanced Prostate Cancer: Management NOCR Annual Meeting, Las Vegas,
NV, 3/6/08
176. "Management of Prostate Cancer": AUA Educational Course, Course Director AUA
Annual Meeting: AUA Educational Course, Course Director, AUA Annual Meeting,
Orlando, FL 5/20/08
177. "GU Cancers" Columbus CCOP 2008 ASCO Review Columbus, OH 6/20/08
178. "Androgen deprivation therapy and bone and metabolic consequences" " "
Management of Advanced Bladder Cancer"
179. "Sequence and combination therapy options in advanced renal cancer" Perspectives in
Urologic Oncology, Chicago, IL 9/5, 9/6/08
180. "Systemic Management of Advanced Prostate Cancer" Aultman Cancer Conference,
Canton, OH 9/26/08
181. "Picking the right therapy for the right patient with metastatic renal cancer"
"Update on systemic therapy of renal cancer" Fourth Annual Oncology Congress, San
Francisco, CA 9/27/08
182. "Targeted Therapeutics in Urothelial Cancer" ASCO GU Symposium, Orlando FL
2/27/09
183. "Evolving Systemic Therapy Options For Prostate Cancer" Jefferson University, Kimmel
Cancer Center, Philadelphia, PA 3/13/09
184. "Evolving Systemic Therapy Options For Prostate Cancer" University of Cincinnati Prostate
Cancer Symposium, Cincinnati, OH 8/15/09
185. "Systemic Therapy for Advanced Prostate Cancer" IPGCC Conference, Athens, Greece
2/23/10
186. "Wither Sipulucel-T" Poster Discussion Session, American Society of Clinical Oncology
Meeting, Chicago, IL 6/7/10
187. "Urothelial Cancer" M.D. Anderson Hematology/Oncology Board Review, Houston, TX
9/20/10
188. "Systemic Therapy Options for Advanced Prostate Cancer" Karmonas Cancer Center,
Detroit, MI 10/6/10
189. "Integrating Novel Systemic Therapy Options for in the Management of Advanced Prostate
cancer" Valley Hospital, Paramus NJ 10/19/10
190. "TAK-700 in Advanced Prostate Cancer" Chemotherapy Foundation Symposium NY, NY
10/12/10
191. "Integrating Novel Systemic Therapy Options for in the Management of Advanced Prostate
cancer" Society of Urologic Oncology Bethesda, MD 12/10/10
192. "Drug Development in Advanced Renal Cancer: Issues of Signal to Noise Ratio in an
Emerging "Chronic Disease" Renal Cancer Oral Abstract Discussant, ASCO GU
Orlando, FL 2/19/11
193. "Integrating Novel Systemic Therapy Options for in the Management of Advanced Prostate
cancer" Moffit Cancer Center Prostate Cancer Symposium, Tampa FL 5/9/11
- "Evolving Systemic Therapy Options for Advanced Prostate Cancer" Chinese Society of Clinical
Oncology, Xiamen China 9/17/11

Presentations (cont):

194. “Renal and Urothelial Cancers” Dana Farber Master Class New York 10/29/11
195. “Renal and Urothelial Cancers” “Prostate Cancer” Dana Farber Master Class Miami, FL 11/12/11
196. “Advanced Urothelial Cancer: So Many Drugs, So Little Progress” GU Seminar series, Dana Farber Cancer Center, Boston MA 3/7/12
197. “Prostate Cancer: Current Status, Recent Developments” Martin & Ethel Sirotkin Cancer Lecture Series Cleveland Clinic Westin, Westin FL 3/9/12
198. “Integrating Novel agents in the Management of Castrate-Resistant Metastatic Prostate Cancer” Community Cancer Research Foundation Cancer Review, Munster IN 3/17/11
199. “Management of Prostate Cancer: A Case-Based Approach” AUA Course, American Urologic Association meeting, Atlanta, GA 5/21/12
200. “The Evolving Management Paradigm of Castration-Resistant Prostate Cancer” NYU Hematology/Oncology Grand Rounds, NY, NY 6/22/12
201. “Advances in the Management of Castration-Resistant Prostate Cancer” Prostate Cancer Research Institute 2012 Annual Meeting, Los Angeles, CA 9/8/12
202. “Evolving Management Paradigm of Castration-Resistant Prostate Cancer” University of Cincinnati, Hematology/Oncology Grand Rounds Cincinnati, OH 9/14/12
203. “Castration-resistant prostate cancer, evolving management into a chronic disease”
204. Roswell Park Cancer Center Grand Rounds Buffalo, NY 10/19/12
205. “Advanced in Management of Prostate Cancer” “Evolving Therapeutics in Renal and Bladder Cancers” Dana Farber Master Class NY, NY 10/26/12
206. “Evolving Therapeutics in Renal and Bladder Cancers” Dana Farber Master Class Fort Lauderdale, FL 11/2/12
207. “Advances in management of castration resistant prostate cancer” Virginia Oncology Associates 13th Annual Educational Conference Virginia Beach VA, 11/10/12
208. “Castration-resistant prostate cancer, evolving management into a chronic disease” Hematology/Oncology Grand Rounds, Rush University Medical Center, 1/23/13
209. “Prostate Cancer Screening: The Controversy” Western Michigan Cancer Center Annual Cancer Conference Kalamzoo, MI 2/1/13
210. “Evolving Management Paradigm of Castration-Resistant Prostate Cancer” Methodist Hospital, Philadelphia, PA 3/20/13
211. “Management of Prostate Cancer: A Case-Based Approach” AUA Course, American Urologic Association meeting, San Diego, CA 5/05/13
212. “Castration resistant prostate cancer evolving management” University of Mass hematology/oncology Grand Rounds, Worcester, Mass 9/19/13
213. “Castration resistant prostate cancer evolving management” Aultman Cancer Center, Canton OH 10/18/13
214. “Evolving Management Paradigm of Castration-Resistant Prostate Cancer” Grand Rounds, Texas HealthResource Dallas Presbyterian Hospital, Dallas, Tx 11/6/13
215. “Oreternol (TAK 700) in Castration Resistant Metastatic Prostate Cancer” Chemotherapy Symposium, NY 11/8/13

Presentations (cont):

216. “Results from a phase 3, randomized, double-blind, multicenter, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy (ELM-PC 5 trial)” ASCO GU, San Francisco, CA, 1/31/14
217. “Novel Anti-androgen Therapies for Castration-Resistant Prostate Cancer” and “Immunotherapeutic Approaches for Advanced Prostate Cancer” Annual Interdisciplinary Prostate Cancer Conference NY, NY 3/15/14
218. “Evolving management of Castration-Resistant Prostate Cancer” Ohio Urologic Society Meeting, 3/22/14 Cincinnati OH
219. “Management of Prostate Cancer: A Case Based Approach with Emphasis on Integrating New Molecular Diagnostics into Clinical Practice “ AUA Course, American Urologic Association Meeting, Orlando FL 5/18/14
220. “Evolving Therapeutics in Renal and Bladder Cancers” Dana Farber Master Class Chicago, IL, 4/23/14
221. “Evolving Therapeutics in Renal and Bladder Cancers” Dana Farber Master Class San Francisco, CA 5/17/14
222. “Bone targeted management of castration resistant metastatic prostate cancer, Methodist Hospital, Thomas Jefferson University, Philadelphia PA 5/21/14
223. “Current status of Systemic Therapy for Castration-Resistant Prostate Cancer”, “Role of perioperative therapy in advanced bladder cancer”, Current status of systemic therapy in advanced renal cancer. “ Hospital Albert Einstein GU Oncology Conference, Sao Paulo Brazil 8/9/14
224. “Evolving Insights for Integrating New Treatment Options and Optimizing Outcomes for Advanced Prostate Cancer” Hematology/Oncology Grand Rounds John Stronger Hospital, Chicago IL, 9/4/14
225. “Evolving Insights for Integrating New Treatment Options and Optimizing Outcomes for Advanced Prostate Cancer” Gibbs Cancer Center, Spartanburg SC 12/16/14
226. “Pathologic Response to Neo-adjuvant Systemic Therapy in Muscle-Invasive Bladder Cancer: Implications for Drug Development” AACR, Philadelphia 4/19/15
227. “Highlights of the Oral Prostate Session” ASCO, Chicago 6/1/15
228. “Prostate Cancer for the Internist: 2015” Medicine Grand Rounds UVA 8/5/15
229. “Evolving Management of Renal and Urothelial Neoplasms” Dana Farber Master Class for Oncologists, NY, NY 10/24/15
230. “Bladder and Renal Cancers: Best Practices for Treatment Selection and a Look towards the Future, Dana Farber Master Class, Chicago, IL 4/30/16
231. “Primary Analysis of IMvigor210: Atezolizumab in Platinum-Treated
232. “Advanced Urothelial Carcinoma” American Urologic Association Oral Presentation, San Diego CA, 5/8/16
233. “Advanced Prostate Cancer: Incorporating Recent Advances into Current Management Paradigms” Dana Farber Master Class, Los Angeles 5/13/16
- “Updated efficacy and 1-year follow up from IMvigor210: Atezolizumab in platinum treated locally advanced/metastatic urothelial carcinoma” American Society of Clinical Oncology Annual Meeting, Oral presentation Chicago IL, 6/6/16

Presentations (cont):

234. "Highlights of the Oral Prostate Session" American Society of Clinical Oncology Annual Meeting, Chicago IL, 6/7/16
"The Promise of Immunotherapy and Benefits of a Multidisciplinary Team Approach"
2016 Immuno-Oncology Update, Toronto CA 9/23/16
235. "Immunotherapy in Advanced Urothelial Cancer, Panel Discussant PSA Failure, management castration resistant metastatic prostate cancer. VIII international Uro-Oncology Conference, Sao Paulo Brazil 3/24-25/17
236. "Management of Advanced Prostate Cancer" PCRI mid-year conference, Los Angeles, CA 3/26/17
237. "Evolving management of metastatic castration-resistant prostate cancer" MedStar Washington Hospital Center, Washington DC, 4/14/17
238. "Evolving management of metastatic castration-resistant prostate cancer" Brookdale Medical Center, Brooklyn, NY, 5/18/17
239. "Management of Advanced Prostate Cancer" Saginaw VA, Saginaw MI 5/26/17
240. "Evolving management of metastatic castration-resistant prostate cancer" Hem/Onc Grand Rounds, East Carolina University, Greenville NC 9/6/17
241. "Paradigm Shift in Urothelial Cancer: Evolving from a Cytotoxic to an immunomodulatory World" Oncology Grand Rounds, Roswell Park Cancer Institute 9/22/17
242. "Immunotherapy in Advanced Urothelial Cancer" and "Sequencing Therapy in Metastatic Castration-Resistant Prostate Cancer" Multidisciplinary Genitourinary Oncology Course Lisbon, Portugal 10/13-14, 2017
243. "Prostate Cancer for the Internist 2017" Medicine Grand Rounds, Inova Health System, Fairfax, VA 10/24/17
244. "Appraisal of Recent Progress in Metastatic Castration-Resistant Prostate Cancer: Current Trends and Future Directions" Cancer Grand Rounds, Gwinnet Medical Center, Atlanta, GA 12/7/17
245. "Appraisal of Recent Progress in Metastatic Castration-Resistant Prostate Cancer: Current Trends and Future Directions" Hem/Onc Grand Rounds, Einstein Medical Center, Philadelphia PA 12/8/17
246. "How will Today's Presentations Impact Clinical Practice?" ASCO-SITC Symposium, San Francisco, CA 1/26/18
247. "Appraisal of Recent Progress in Metastatic Castration-Resistant Prostate Cancer: Current Trends and Future Directions" Grand Grounds Cape Fear Valley Cancer Center, Fayetteville NC 3/14/18
248. "Management of Advanced Prostate Cancer" Grand Rounds Huntington Hospital, Huntington, NY 4/11/18
249. "Appraisal of Recent Progress in Metastatic Castration-Resistant Prostate Cancer: Current Trends and Future Directions" Maimonides Cancer Center, Brooklyn, N.Y. 4/11/18
250. "Evidence-Based Management of Advanced and Metastatic Urothelial and Renal Cancers" Dana Farber Master Class San Francisco, CA 4/28/18
251. Evidence-Based Management of Advanced and Metastatic Urothelial and Renal Cancers" Dana Farber Master Class Chicago, IL, CA 5/11/18
- "Crossfire: Controversies in Urology: Prostate Cancer" American Urologic Association Meeting San Francisco, CA 5/18/18.

Presentations (cont):

252. "Leveraging the Immunologic Dysfunction in Bladder Cancer Through Combination Systemic Therapy" Cancer Center Grand Rounds UT San Antonio Mays Cancer Center, San Antonio, Tx 10/10/18
253. "Leveraging the Immunologic Dysfunction in Bladder Cancer Through Combination Systemic Therapy" Hematology/Oncology Grand Rounds Virginia Commonwealth University. Richmond, VA 11/20/18
254. "Update on Issues in the Management of Advanced Prostate Cancer" JADPRO annual Conference Hollywood FL 12/5/18
255. "Leveraging the Immunologic Dysfunction in Bladder Cancer Through Combination Systemic Therapy" Cancer Center Grand Rounds University of Maryland Cancer Center, Baltimore, MD. 12/20/18
256. "Evolving management of Non-Metastatic Castration-Resistant Prostate Cancer" Blumenthal Cancer Center, Paramus NJ 3/14/19
257. "Immunotherapy for Advanced Urothelial Cancer" PER GU oncology Meeting, NY, NY 3/15/19
258. "Unraveling the Complex Treatment Landscape of Prostate Cancer: Guidance for Delivering Evidence-Based, Patient-Centered Care" Virginia Urologic Association, Hot Springs VA 4/6/19
259. "Evolving Management of Advanced renal and urothelial cancers" Dana Farber Master Class Los Angeles, CA 4/27/19
260. "Evolving Management of Advanced renal and urothelial cancers" Dana Farber Master Class Chicago, IL 5/20/19
261. "Immune-related therapy toxicity and its management" Teramana Cancer Center, Steubenville, OH 6/28/19
262. "Androgen Deprivation Therapy Related Toxicity and Issues in the Management of Hormone Sensitive Metastatic Prostate Cancer" Hem/Onc Grand Rounds, MedStar, Georgetown. Washington DC, 9/13/19
263. "Androgen Deprivation Therapy Related Toxicity and Issues in the Management of Hormone Sensitive Metastatic Prostate Cancer" Medicine Grand Rounds, Holy Name Hospital, Teaneck NJ, 9/24/19
264. "Prostate Cancer: Emerging Strategies for Individualized Management" and Bladder nd Renal Cancers: Treatment Selection in an Evolving Therapeutic Landscape" Dana Farber Master Class, NY, NY 10/26/19
265. "Advances in Prostate Cancer Management" Mid Atlantic Section American Urologic Association Meeting Pocono, PA 10/24/19
266. "Therapeutic Developments in Advanced Prostate Cancer" Virginia Oncology Associates 20th Annual Educational Conference Norfolk, VA 11/9/19
267. "Immune Therapy Related Toxicity" Sentara Rockingham Memorial Hospital, Harrisonburg, VA Virtual Presentation 5/14/20
268. "Treatment Selection in Renal Cell and Urothelial Carcinoma: Integrating Novel Agents into Daily Practice" Dana Farber Master Class, Virtual Presentation 11/13/20
269. "Front line therapy for advanced urothelial cancer" "Front-line therapy for advanced renal cancer" Onc Live Institutional Perspectives in GU Cancer Virtual 3/3/21

Presentations (cont):

- 270. "Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence In Kidney Cancer Management During the COVID-19 Pandemic" SUNY Downstate in Brooklyn, NY, Virtual Presentation 4/30/21
- 271. "Advanced Treatment Strategies in Prostate Cancer: A Closer Look at the Current and Emerging Therapeutic Options. NAMCP Spring Managed Care Forum, virtual presentation 4/22/21
- 272. "Improving Survival for Veterans with Bladder Cancer-Translating New Knowledge into Clinical Practice" University of Florida VA, virtual presentation 6/11/21
- 273. "Management of Castration-Sensitive Metastatic Prostate Cancer" Advances in the Management of Prostate, Kidney and Bladder Cancers Medstar Health, Washington D.C. Virtual Presentation 6/18/21
- 274. "Immunotherapeutics in Urologic Neoplasms" Whats Next? 2nd ECO Cancer Immunotherapy Breakthrough Conference, Madrid Spain, Virtual Presentation 7/1/21
- 275. "Advanced Kidney Cancer: Therapeutic Update" 21th Future Directions in Urology Symposium 8/8/21 Charlottesville, VA
- 276. "Improving Survival for Veterans with Bladder Cancer-Translating New Knowledge into Clinical Practice" University of Iowa VA, virtual presentation 9/17/21
- 277. "Adjuvant Therapy for Kidney Cancer: Are we There Yet? Society of Urologic Oncology meeting, Orlando FL 12/3/21
- 278. "Innovations in Prostate Cancer Management: Taking a Personalized Approach to Optimal Treatment" 2022 Spring Managed Care Forum, Orlando Florida 4/21/22
- 279. "Treatment Selection In Renal Cell and Urothelial Carcinoma: Integrating Novel Agents into Daily Practice" Dana Farber Master Class, Chicago, IL 10/21/22
- 280. "Triplet Therapy in mHSPC:Nope" AUA Plenary Session, Chicago IL, 4/28/23
- 281. "Evolving Role of Immunotherapy in the Management of Urothelial Cancer" Society of Government Service Urology Conference, Norfolk VA 1/20/24
- 282. "Sequencing Therapy in mCRPC: When you get to the fork in the road take it" Beaumont Hospital, Hematology/Oncology Grand Rounds (Virtual), Royal Oaks, MI 5/21/24
- 283. "“Navigating Treatment Advances for Prostate Cancer: Integrating the Latest Evidence-Based Approaches for Optimal Health Outcomes”.National Association of Managed Care Physicians Fall Conference, Las Vegas, NV 11/8/24
- 284. "Perioperative Chemotherapy for Upper Track Urothelial Cancer" International Bladder Cancer Update, Dallas, TX 12/7/24
- 285. "Evolving Role of PARP inhibitors and Genomics in Advanced Prostate Cancer" George Washington University Cancer Center Grand Rounds (Virtual) 4/25/25