

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

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

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Ipsen Biopharm Ltd. (“Ipsen”) responds to the petition of CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, “CSPC”). As set forth below, CSPC fails to show that the challenged claims of U.S. Patent No. 11,344,552 (“the ’552 patent”), which recite a multi-drug chemotherapy regimen for treatment of metastatic pancreatic cancer, composed of four specific drugs, administered in four specific doses and in a recited frequency, are obvious over FOLFIRINOX. FOLFIRINOX, repeatedly characterized by CSPC as the “gold standard” treatment at the time of invention, is composed of a different four-drug combination of chemotherapy drugs, in different recited doses.

Even assuming that a person of ordinary skill (“POSA”) would have been motivated to modify the “gold-standard,” CSPC’s obviousness challenge relies on the unlikely premise that, in order to address toxicity concerns, a POSA would have been motivated to make four, specific changes to FOLFIRINOX, simultaneously:

- (1) reduction of 85 mg/m² oxaliplatin to 60 mg/m² oxaliplatin;
- (2) removal of the 400 mg/m² bolus dose of 5-FU;
- (3) replacement of free irinotecan with liposomal irinotecan; and
- (4) dosage of liposomal irinotecan at 60 mg/m².

It is unlikely a POSA would be so motivated for at least the reason that a POSA would have known of numerous approaches to modifying FOLFIRINOX in order to address toxicity concerns. None of these approaches taught or suggested—as CSPC urges would have been obvious—the extreme measure of introducing a new component, in a new dose, to create a new combination therapy for treating pancreatic cancer.

CSPC’s obviousness argument relies on impermissible use of hindsight. Indeed, deposition testimony by its expert, Dr. Ratain, reveals the hindsight-driven approach he took in assessing alleged obviousness. Dr. Ratain testified, among other things, that he began his analysis with FOLFIRINOX based on its “similarity” to the ’552 patent claims and, further, that his review of the ’552 patent’s specification and/or claim elements drove selection of other asserted references. Ex. 2073 at 29:4-20; 35:12-36:5; 39:24-41:16. CSPC and Dr. Ratain’s failure to articulate—as the obviousness inquiry requires—why a POSA would have been motivated to make all of these modifications at once also evidences the hindsight-driven nature of their obviousness challenge.

CSPC presents its obviousness argument piecemeal, addressing a single modification at time. But this is improper, and CSPC’s piecemeal arguments fail for several reasons.

First, CSPC ignores that the Conroy references—and subsequent references by the same co-authors—explicitly define FOLFIRINOX as comprising 85 mg/m² oxaliplatin, not the claimed 60 mg/m². CSPC’s argument to the contrary relies on a selective and incorrect interpretation of Conroy and other references.

Second, CSPC ignores the prior art as a whole, which discloses numerous approaches for addressing toxicity concerns with FOLFIRINOX, none of which lead to the claimed invention. For instance, it was known that dose reduction of a single component—as opposed to the multiple dose reductions and replacement of one cytotoxic ingredient with another, as CSPC urges—sufficiently addressed toxicity concerns.

Third, CSPC improperly relies on data for one-, two-, or three-drug combination therapies as alleged motivation to pursue the ’552 patent’s novel four-drug combination therapy with a reasonable expectation of success. But preclinical or early-phase data from these different therapies or drug combinations would not have motivated or reasonably inspired success in the claimed therapy – particularly given the low likelihood of success in this particular field.

CSPC’s arguments fail for other reasons, as outlined in greater detail herein. The Board should reject CSPC’s obviousness challenge in its entirety.

II. BACKGROUND

A. Treatment of Metastatic Pancreatic Cancer

Pancreatic cancer is one of the leading causes of cancer-related deaths in the U.S. Due to its location and the relative lack of predictive diagnostic criteria, it is most often diagnosed at an advanced stage. Ex. 2076 (Oberstein Declaration) ¶¶ 47-50. In patients diagnosed with metastatic pancreatic cancer, the median overall survival is less than one year, and the five-year survival rate is approximately 2%. *Id.*

The goal of treatment, especially first-line treatment, is to administer the most efficacious dose. Ex. 2076 ¶ 50; *see also, e.g.*, Ex. 1012 at 2 (describing that, for colorectal cancer, “a more active first-line treatment can be more effective”). But the treatment agents are toxic, which complicates what constitutes “effective” treatment, particularly when multiple toxic agents are administered as a combination therapy. *See* Ex. 2076 ¶¶ 262-66. Toxicity issues that present during treatment may necessitate dosage adjustment after administration of a starting dose of therapy, which may in turn compromise efficacy. *See id.* at ¶¶ 62, 262-66.

Advances in treatment for metastatic pancreatic cancer have been based on showings of incremental improvements in survival. *See* Ex. 2076 ¶¶ 47, 51-55; *see also* Ex. 1009 at 5 (“[T]he hallmark of a truly successful systemic therapy for pancreatic cancer is an ability to prolong survival.”). In 1997, gemcitabine became

the first-line choice for treatment of metastatic pancreatic cancer. Ex. 2076 ¶ 52. FOLFIRINOX became the new first-line standard following clinical trial results showing safety and efficacy of the FOLFIRINOX regimen over gemcitabine. *Id.* at ¶ 56.

FOLFIRINOX refers to a four-drug combination therapy, comprised of four chemotherapy drugs, each in a recited dose: (1) 85 mg/m² oxaliplatin; (2) 180 mg/m² irinotecan; (3) 400 mg/m² leucovorin (“LV”); and (4) 400 mg/m² bolus of 5-fluorouracil (“5-FU”), followed by a 2400 mg/m² continuous infusion of 5-fluorouracil. *Id.*; Ex. 1003 at 3.

After FOLFIRINOX emerged as a preferred first-line treatment option, variations on the dosage(s) of its constituent components were used in order to address dose-limiting toxicity issues. Ex. 2076 ¶¶ 57-63. Generally, these modifications entailed dose reduction of one or more of the four components after the initial dose of treatment. *Id.* In the years following FOLFIRINOX’s adoption as a first-line treatment option, other combination therapies were studied. Efforts to develop new combination therapies failed, but a combination therapy of gemcitabine plus nab-paclitaxel emerged as a treatment option. *Id.* at ¶¶ 64, 216, 302.

B. Onivyde[®], NALIRIFOX, and the '552 Patent

Ipsen's Onivyde[®] (irinotecan liposome injection) is a treatment for metastatic pancreatic cancer. The FDA recently approved Onivyde[®] as a first-line treatment for adult patients with metastatic pancreatic adenocarcinoma. This was based on results from the NAPOLI 3 clinical study, which assessed safety and efficacy of Onivyde[®] relative to the combination therapy of gemcitabine and nab-paclitaxel. Ex. 2076 ¶¶ 65-68.

Onivyde[®]'s first-line treatment regimen, referred to as "NALIRIFOX," is a combination therapy consisting of four different chemotherapy drugs, each administered in specific doses and frequency. *Id.*; *see also* Ex. 2073 (Ratain Deposition) at 19:13-21:6 (CSPC's expert detailing the "specific recipe" claimed by the '552 patent).

The '552 patent covers the four-drug combination therapy of NALIRIFOX.

Claim 1 is representative:

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

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

d. 2,400 mg/m² 5-fluorouracil;

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

Ex. 1001 ('552 patent) at claim 1; *see also* Ex. 2076 ¶¶ 103-09. Claim 12, the other independent claim, recites the same combination therapy for a patient “who has not previously received gemcitabine.” Ex. 1001 at claim 12. Dependent claims 2-11 and 13-15 recite specific sequences for administration of the claimed combination therapy and other formulation details. *Id.* at claims 2-11, 13-15. The '552 patent describes claimed embodiments by reference to starting doses, as claimed. *E.g., id.* at 13:38-46; 30:5-11, Tables 1B-1E. As the Board has found, the '552 patent has an effective filing date of August 21, 2015. Paper 13 at 45.

During prosecution of the '552 patent, Ipsen overcame obviousness challenges based on the same two lead references that CSPC asserts here, namely, Bayever and Conroy. *See* Ex. 1084 at 192-193, 317 (citing Conroy and Bayever in a § 103 rejection); Ex. 1088 at 59-60 (same); Ex. 1097 at 190-191 (same); Ex. 1119 at 11-12 (same); Ex. 2001 at 1 (same). The Examiner specifically raised the argument that CSPC presents here, that dose reduction of oxaliplatin was a “result-effective variable” that supported obviousness. *Compare* Ex. 1084 at 318 (describing “[o]xaliplatin and its amount” as “result effective”) *with* Paper 1 at 46-47 (arguing “the POSA recognized that adjusting the dose of oxaliplatin was a result effective variable subject to routine optimization”). Ipsen ultimately

overcame this argument and submitted evidence of unexpected results, specifically in the form of efficacy and safety of the claimed regimen. Ex. 2076 ¶¶ 120-23.

The '552 patent issued on May 31, 2022.

III. PERSON OF ORDINARY SKILL IN THE ART

For purposes of this Response, Ipsen does not dispute CSPC's proposed definition of a POSA. *See also* Ex. 2076 ¶¶ 129-32.

IV. CLAIM CONSTRUCTION

In an *inter partes* review, the Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a POSA. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Here, a POSA would understand that “treatment” has its plain and ordinary meaning, for example, “the management and care of a patient for the purpose of combating disease or disorder.” Ex. 2017 (Dorland's Dictionary) at 3; *see also* Ex. 2018 (Stedman's Dictionary) at 3 (“Medical or surgical management of a patient.”); Ex. 2019 (Taber's Dictionary) at 3 (“1. Medical, surgical, dental, or psychiatric management of a patient. 2. Any specific procedure used for the cure or the amelioration of a disease or pathological condition.”). “Treatment,” as used

in the '552 patent, refers to management and/or care comprising antineoplastic therapy in accordance with the claims and specification.

The '552 patent's intrinsic record supports such plain and ordinary meaning. The claims recite, *inter alia*, “method[s] of treating metastatic adenocarcinoma of the pancreas in a human patient” comprising “administering an antineoplastic therapy” that consists of the recited drugs, in each of their recited dosages, in accordance with a recited schedule. *See* Ex. 1001 at claim 1. U.S. Provisional Application No. 62/208,209 (“the '209 application”), which the '552 patent incorporates in its entirety (Ex. 1001 at 1:9-17), defines “effective amount” or “therapeutically effective amount” as “an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result.” Ex. 1015 at [0037]; *see also id.* at [0076]-[0080]. This is consistent with Dr. Ratain's testimony. *See* Ex. 2073 at 91:16-23 (defining “effective” as “to treat one or more symptoms of the disease and/or to reduce the size of the tumor or reduce the rate of growth of the tumor.”). A POSA would understand that the claimed methods of treatment comprise administering an antineoplastic therapy consisting of administration of the recited drugs, in the recited doses and frequency, to provide more than a *de minimis* therapeutic benefit or efficacy. *See* Ex. 2076 ¶¶ 133-45.

The Board has found that, here, “the ordinary understanding of a claim reciting a ‘method of treating adenocarcinoma of the pancreas’ that comprises

‘administering an antineoplastic therapy to the patient’ in order ‘to treat the metastatic adenocarcinoma of the pancreas’ is that the ‘treatment’ would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.” Paper 13 at 14. Although the verbiage “de minimis” does not appear in the specification, the intrinsic record supports such construction. *See, e.g.*, Ex. 1015 at [0037]; *see also id.* at [0076]-[0080]; *see also* Ex. 2076 ¶¶ 133-45. Whether under Ipsen’s proposed construction or the Board’s construction, CSPC fails to show obviousness for the reasons discussed herein.

Ipsen disagrees with CSPC’s proposed “construction,” which would require simply administration with no expectation of therapeutic benefit or efficacy. *See* Paper 1 at 26-30. Such “construction” finds no support in the intrinsic record, which—to the contrary—describes the claimed methods in terms of their clinical effects. The ’552 patent specification’s examples describe such clinical effects, including in the recited patient population. *See, e.g.*, Ex. 1001 at 21:30-43:19 (Example 3, “Treatment of Pancreatic Cancer”), 43:21-46:16 (Example 4, “Tolerability of Antineoplastic Therapies in Human Clinical Trial”). During prosecution, Ipsen also cited evidence of the claimed treatment methods’ clinical effects, such as prolonged or progression-free survival, safety, and tolerability. *See, e.g.*, Ex. 2016 (February 25, 2022 Remarks); Ex. 1119 at 151-54. A POSA would therefore understand that the plain and ordinary meaning of “treat” and

“treatment” is more than simply the administration of the recited components, in the recited doses and frequency. *See* Ex. 2076 ¶¶ 133-45.

V. THE CHALLENGED CLAIMS HAVE AN EFFECTIVE FILING DATE OF AUGUST 21, 2015

The '552 patent has an effective filing date of August 21, 2015, which is the filing date of its earliest priority application, the '209 application. The written-description requirement is met where the disclosure “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '209 application, the entirety of which is incorporated by reference in the '552 patent specification (Ex. 1001 at 1:9-17) reasonably conveys to a POSA that the inventors were in possession of the claimed methods of treatment, which provide more than a *de minimis* therapeutic or clinical benefit as of its filing date. *See* Ex. 2076 ¶¶ 124-28.

VI. CSPC’S ASSERTED REFERENCES

A. Conroy

Conroy appears to be an article titled, “FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer.” Ex. 1003 at 1. CSPC has not produced evidence sufficient to establish that Conroy is a printed publication, including the date by which it became publicly available. Conroy was discussed at length during

prosecution of the '552 patent.

Conroy describes a clinical study on the safety and efficacy of FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer. Ex. 1003 at 1. Conroy defines FOLFIRINOX as the biweekly administration of (1) 85 mg/m² oxaliplatin, followed by (2) 400 mg/m² leucovorin, (3) 180 mg/m² irinotecan, and (4) fluorouracil administered as a 400 mg/m² bolus dose followed by a 2400 mg/m² infusion. *Id.* at 3.

Conroy reports that FOLFIRINOX demonstrated favorable efficacy outcomes over gemcitabine. Specifically, “[t]he median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 months vs. 6.8 months).” *Id.* at 6. Conroy notes that “the safety profile of FOLFIRINOX was less favorable than that of gemcitabine.” *Id.* at 8. But, “[d]espite the higher incidence of adverse events associated with the FOLFIRINOX regimen, a significant increase in the time to definitive deterioration of the quality of life was observed in the FOLFIRINOX group as compared with the gemcitabine group.” *Id.*

As Dr. Oberstein explains, a POSA would not understand Conroy to provide any teaching as to a combination therapy that includes liposomal irinotecan, at any dose, or oxaliplatin at the claimed dose. Ex. 2076 ¶¶ 146, 149-53, 161. To the

extent that certain patients received dose reductions, Conroy does not report outcomes specific to any such patients. *Id.* at ¶ 153.

B. Conroy Protocol and Appendix

Conroy Protocol appears to be a translation titled, “Protocol.” Ex. 1004 at 1. CSPC did not provide, as required under 37 C.F.R. § 42.63(b), a certification of translation of Conroy Protocol along with its Petition on January 17, 2025. *See* Paper 1, Ex. 1004. Nor has CSPC produced evidence that Conroy Protocol is a printed publication, including the date by which it became publicly available.

Conroy Appendix appears to be a document titled, “Supplementary Appendix.” Ex. 1017 at 1. CSPC has not produced evidence sufficient to establish that Conroy Appendix is a printed publication, including the date by which it became publicly available.

Conroy Protocol and Conroy Appendix purport to provide further detail on the study reported in Conroy. Conroy Protocol, like Conroy, describes FOLFIRINOX as the biweekly administration of (1) 85 mg/m² oxaliplatin, followed by (2) 400 mg/m² leucovorin (folinic acid), (3) 180 mg/m² irinotecan, and (4) fluorouracil (5-FU) administered as a 400 mg/m² bolus dose followed by a 2400 mg/m² infusion. In particular, Conroy Protocol describes “Folfirinox” in terms of the initial, or “defining,” doses:

Treatment A: Folfirinox

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

Ex. 1004 at 14; *see also id.* at 15 (“Treatment will begin with oxaliplatin 85 mg/m² IV infused over 2 hours”); *see also id.* at 42, 57, 76-77. Conroy Appendix indicates that the results reported in Conroy are based on data obtained at baseline, prior to treatment. *See, e.g.,* Ex. 1017 at 9 (“The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.”); *id.* at 16 (Suppl. Fig. I reporting 171 patients in the intent-to-treat arm, 4 of which did not receive treatment); Ex. 1003 at 4 (“The intention-to-treat population included 171 patients in each group.”). Together, Conroy Protocol and Conroy Appendix indicate that all of the patients in the FOLFIRINOX arm of the study who received treatment received FOLFIRINOX.

CSPC and Dr. Ratain rely on the dose-adjustment guidelines of Conroy Appendix and Conroy Protocol. Paper 1 at 16; Ex. 1002 at ¶¶ 104-06. These guidelines specify certain dose adjustments of one or more components of FOLFIRINOX after initiation of treatment, contingent upon the occurrence of certain pre-specified events. *See* Ex. 1004 at 16-20; Ex. 1017 at 3-7. The dose-adjustment guidelines do not recommend oxaliplatin dose reduction in all

instances, nor do they recommend 5-FU bolus removal in all instances. *See* Ex. 1004 at 16-20; Ex. 1017 at 3-7. Nor do the dose-adjustment guidelines instruct any preemptive (i.e., prior to administration of the initial dose) dose reduction. *See* Ex. 1004 at 16-20; Ex. 1017 at 3-7.

As Dr. Oberstein explains, a POSA would not understand Conroy Appendix and/or Conroy Protocol to teach that FOLFIRINOX consists of an oxaliplatin dose other than 85 mg/m². Ex. 2076 ¶¶ 147-48, 154-60.

C. Bayever

Bayever is a PCT application titled, “Methods for Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan,” published as WO 2013/188586 and bearing an international publication date of December 19, 2013. Ex. 1006 at 1-2. Bayever was discussed at length during prosecution of the ’552 patent.

Bayever describes the challenges associated with treating metastatic pancreatic cancer. *See* Ex. 2076 ¶ 170. Bayever characterizes advances in the treatment of metastatic cancer in terms of incremental prolongation of survival. *See id.* at ¶ 171. Bayever describes the need for new treatments, particularly against the backdrop of failed clinical trials. *Id.* at ¶ 172.

Bayever describes treatments that comprise liposomal irinotecan, as well as studies of liposomal irinotecan and its properties. *See id.* at ¶¶ 173-79. Bayever's Example 7 describes, for example, a Phase 3 study of different treatment arms:

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

Ex. 1006 at 26-27. Arm A and Arm C comprise liposomal irinotecan, in different doses. *Id.* None of the treatment arms comprise oxaliplatin, in any dose.

As Dr. Oberstein explains, a POSA would not understand Bayever to teach a combination therapy that includes liposomal irinotecan and oxaliplatin, much less in the dosages claimed by the '552 patent. Ex. 2076 ¶¶ 174-80.

D. Saif

Saif appears to be an article titled, "MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastatic Pancreatic Cancer." Ex. 1007 at 1. CSPC has not produced evidence sufficient to establish that Saif is a printed publication, including the date by which it became publicly available.

Saif purports to describe NAPOLI-1, a study of liposomal irinotecan in combination with 5-FU and LV as a second-line treatment for metastatic pancreatic cancer. Ex. 1007 at 1-2. As Saif reports, this combination therapy demonstrated a 1.9-month improvement in survival as compared to 5-FU and LV alone, as well as a statistically significant improvement in progression-free survival. Ex. 1007 at 1. Saif does not disclose the dose of liposomal irinotecan, or any other component of the NAPOLI-1 treatment. As Dr. Oberstein explains, a POSA would not understand Saif to suggest replacing irinotecan in FOLFIRINOX with liposomal irinotecan but rather that the combination of oxaliplatin and irinotecan presents distinct toxicity concerns. Ex. 2076 ¶¶ 181-85; *see also* Ex. 2073 at 121:14-17.

E. Ko

Ko appears to be an article titled, “A multinational phase 2 study of nanoliposomal irinotecan sucrosfate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer.” Ex. 1008 at 1. CSPC has not produced evidence sufficient to establish that Ko is a printed publication, including the date by which it became publicly available.

Ko describes a study of liposomal irinotecan monotherapy as a second-line treatment in patients with pancreatic cancer. *See* Ex. 1008 at 1; Ex. 2073 at 116:21-23. Ko’s study evaluated a different dose of liposomal irinotecan than claimed by the ’552 patent. *Compare id.* at 2 (120 mg/m² every three weeks) *with*

Ex. 1001 at claim 1 (reciting 60 mg/m² every two weeks). Ko reports that liposomal irinotecan monotherapy showed evidence of antitumor activity, but that the majority of patients experienced at least one grade 3 or higher adverse event. Ex. 1008 at 5. Of the grade 3 or higher adverse events, neutropenia was the most frequently reported. *Id.* at 2 (Table 2). Ko, which discusses the study of liposomal irinotecan as monotherapy, does not even purport to discuss the effect if any of liposomal irinotecan in combination with oxaliplatin, 5-FU, or LV.

As Dr. Oberstein explains, a POSA would not understand Ko to teach or suggest replacing irinotecan with liposomal irinotecan. Ex. 2076 ¶¶ 186-92. To the extent that Ko suggests further study of liposomal irinotecan, it is not as a component of FOLFIRINOX. *Id.* at ¶ 192.

F. Mahaseth

Mahaseth appears to be an article titled, “Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma.” Ex. 1005 at 1. CSPC has not produced evidence sufficient to establish that Mahaseth is a printed publication, including the date by which it became publicly available.

Mahaseth describes a study of modifications to FOLFIRINOX that do not involve liposomal irinotecan, in any dose, or oxaliplatin at the claimed dose. *See* Ex. 1005 at 1. Rather, the modifications in Mahaseth consisted of: (1) removal of

the 5-FU bolus and (2) administration of hematopoietic growth factor, specifically 6 mg of pegfilgrastim, as second-line therapy for patients whose cancer had progressed after gemcitabine-containing first-line treatment. *Id.* at 1-2. This modified regimen otherwise maintained FOLFIRINOX's 85 mg/m² oxaliplatin, 180 mg/m² irinotecan, 400 mg/2 LV, and 2400 mg/m² 5-FU. *Id.* at 2. As Dr. Oberstein explains, a POSA would not understand Mahaseth to teach or suggest modification to FOLFIRINOX other than removal of the 5-FU bolus and adding a hematopoietic growth factor. Ex. 2076 ¶¶ 162-68.

G. Cantore

Cantore appears to be an article titled, "Combined Irinotecan and Oxaliplatin in Patients with Advanced Pre-Treated Pancreatic Cancer." Ex. 1009 at 1. CSPC has not produced evidence sufficient to establish that Cantore is a printed publication, including the date by which it became publicly available.

Cantore appears to predate Conroy and the emergence of FOLFIRINOX as the first-line standard by over six years. *Compare id.* at 1 ("Accepted after revision: February 6, 2004") with Ex. 1003 at 1 (bearing a publication date of May 12, 2011). Accordingly, Cantore does not reflect all information that would have been available to a POSA as of the effective filing date of August 21, 2015. CSPC's expert, Dr. Ratain, testified that he only identified Cantore after counsel "asked [him] are there any references to specifically disclose an oxaliplatin dose of

60 milligrams per meter squared, and so [he] found this regimen.” Ex. 2073 at 40:9-41:16. References that appear to be more recent than Cantore describe studies of oxaliplatin at higher doses than claimed by the ’552 patent. *See* Ex. 2076 ¶¶ 199-200.

Cantore describes a study of a combination therapy that does not include liposomal irinotecan, 5-FU, or LV. The authors of Cantore conclude that higher doses of oxaliplatin than those claimed by the ’552 patent should be studied. *Id.* at 5 (“Future studies should try *higher doses* of irinotecan and *oxaliplatin*.”) (emphasis added). As Dr. Oberstein explains, Cantore does not teach or suggest a combination therapy that comprises liposomal irinotecan, at any dose, much less in combination with 60 mg/m² oxaliplatin. Ex. 2076 ¶¶ 193-200.

H. Masi

Masi appears to be an article titled, “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.” Ex. 1012 at 1. CSPC has not produced evidence sufficient to establish that Masi is a printed publication, including the date by which it became publicly available.

Masi appears to predate Conroy and the emergence of FOLFIRINOX as the first-line standard of treatment of metastatic pancreatic cancer by over six years. *Compare id.* at 1 (“accepted 12 July 2004”) *with* Ex. 1003 at 1 (bearing a

publication date of May 12, 2011). Accordingly, Masi does not reflect all information that would have been available to a POSA as of the effective filing date of August 21, 2015.

Masi describes modifications to FOLFIRINOX that do not include liposomal irinotecan, at any dose, or oxaliplatin in the claimed dose. *See, e.g.*, Ex. 2073 at 102:15-20. Nor is the study described in Masi directed to the treatment of pancreatic cancer. As Dr. Oberstein explains, a POSA would not understand Masi to teach or suggest modification to Conroy's FOLFIRINOX regimen, e.g., replacement of irinotecan with liposomal irinotecan or dose adjustment(s) of other component(s), much less with any reasonable expectation of success. Ex. 2076 ¶¶ 201-09.

I. Ginocchi

Ginocchi appears to be an abstract titled, "Modified FOLFOXIRI in Advanced Pancreatic Cancer." Ex. 1016 at 1. CSPC has not produced evidence sufficient to establish that Ginocchi is a printed publication, including the date by which it became publicly available.

Ginocchi describes modifications to FOLFIRINOX that do not involve liposomal irinotecan, at any dose, or oxaliplatin in the claimed dose. Ginocchi's study evaluated tolerability and activity of a treatment regimen consisting of irinotecan 150 mg/m², 5-FU 2800 mg/m², LV 400 mg/m², and oxaliplatin 85

mg/m² administered biweekly. Ex. 1016 at 1. This modified regimen otherwise maintained FOLFIRINOX's doses of oxaliplatin and leucovorin. *Id.* (“Folinic acid and oxaliplatin remained unchanged.”). As Dr. Oberstein explains, a POSA would not understand Ginocchi to teach or suggest a combination therapy that comprises liposomal irinotecan, at any dose, much less in combination with the other claimed components, in the claimed doses. Ex. 2076 ¶¶ 210-13.

J. Carnevale

Carnevale appears to be an article titled, “MM-398 (nanoliposomal irinotecan): emergence of a novel therapy for the treatment of advanced pancreatic cancer.” Ex. 1013 at 1. CSPC has not produced evidence sufficient to establish that Carnevale is a printed publication, including the date by which it became publicly available.

Carnevale purports to summarize studies involving liposomal irinotecan, none of which study the '552 patent's claimed combination therapy. *See* Ex. 1013. As Dr. Oberstein explains, a POSA would not understand Carnevale to teach or suggest anything beyond the disclosures of Saif and Ko and, if anything, reflects that the likelihood of success in developing new treatments for pancreatic cancer is particularly low. Ex. 2076 ¶¶ 214-216.

VII. LEGAL STANDARD

CSPC bears the burden to show “with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring inter partes review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden never shifts to Ipsen. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

VIII. GROUND 1: CPSC FAILS TO SHOW THAT CLAIMS 1, 3-6, AND 8-14 ARE OBVIOUS OVER ITS ASSERTED REFERENCES

Even assuming that a POSA would be motivated to modify what CSPC repeatedly describes as the then-prevailing “gold standard,” CSPC’s obviousness theory rests on the proposition that a POSA would have had to be motivated to modify FOLFIRINOX in multiple, specific ways in order to arrive at the specifically claimed treatment regimen, namely by:

- (1) reducing 85 mg/m² oxaliplatin to 60 mg/m² oxaliplatin;
- (2) removing the 400 mg/m² bolus dose of 5-FU;
- (3) replacing free irinotecan with liposomal irinotecan; and
- (4) including liposomal irinotecan at a dose of 60 mg/m².

CSPC’s expert, Dr. Ratain, confirmed that modification of FOLFIRINOX to arrive at the claimed method would entail all four of these modifications. Ex. 2073 at 72:9-73:25.

Nowhere in its petition does CSPC articulate motivation to make all four of the required modifications at once. Rather, CSPC argues obviousness in piecemeal, alleging obviousness of one modification at a time. But “[f]ocusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.” *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). And “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). CSPC’s piecemeal obviousness challenge is legally improper and fails for the reasons discussed below.

A. Dr. Ratain’s Deposition Testimony Reveals a Hindsight-Driven Analysis

Only by impermissible use of hindsight, working backwards from the ’552 patent claims, would a POSA have been motivated to make all of these modifications at once. Dr. Ratain confirmed as much, testifying at his deposition that he didn’t “actually look to see” whether FOLFIRINOX was the standard at the time of invention. Ex. 2073 at 29:4-20.¹ Rather, he began his obviousness analysis with FOLFIRINOX, due to its “similarity” to the ’552 patent claims:

¹ At his deposition, Dr. Ratain took a position inconsistent with the opinions expressed in his declaration. In his declaration, Dr. Ratain repeatedly

- Q. And why did you start with FOLFIRINOX?
- A. Because, in reading the claims, I said this is FOLFIRINOX but with the substitution of liposomal irinotecan.
- Q. Okay. So you chose to start with FOLFIRINOX because of its similarity to the claims in the '552 patent, correct?
- A. That's right.

Ex. 2073 at 27:6-13. Such hindsight analysis is improper. *See Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998)) (“Obviousness ‘cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.’”).

refers to FOLFIRINOX as the “gold-standard” treatment. Ex. 1002 at ¶¶ 232, 316. At his deposition, Dr. Ratain “couldn’t tell you that [FOLFIRINOX] was the standard. It was a standard.” Ex. 2073 at 29:4-12. Dr. Ratain’s conflicting testimony on this point renders his opinions unreliable and insufficient basis to conclude obviousness. *See, e.g., N.L.R.B. v. Pittsburgh S.S. Co.*, 337 U.S. 656, 659 (1949) (“[I]n the determination of litigated facts, the testimony of one who has been found unreliable as to one issue may be properly accorded little weight as to the next.”); *Finesse Wireless LLC v. AT&T Mobility LLC*, No. 2024-1039, 2025 WL 2713518, at *4 (Fed. Cir. Sept. 24, 2025) (“When the party with the burden of proof, . . . rests its case on an expert’s self-contradictory testimony, we may conclude the evidence is insufficient to satisfy that standard.”) (citing *Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1349 (Fed. Cir. 2008)).

Dr. Ratain also testified that he relied on the '552 patent's disclosure and/or certain of its claimed elements in selecting other references. When asked why he selected Mahaseth, Dr. Ratain cited the '552 patent specification's discussion of dropping the 5-FU bolus dose. *Id.* at 35:12-36:5. Regarding his selection of Cantore, Dr. Ratain testified that "counsel asked me are there any references to specifically disclose an oxaliplatin dose of 60 milligrams per meter squared, and so I found this regimen." *See id.* at 39:24-41:16. Dr. Ratain's backwards-looking obviousness analysis reveals impermissible use of hindsight. *See Cheese Sys., Inc.*, 725 F.3d at 1352.

B. The Conroy References Do Not Suggest or Teach 60 mg/m² Oxaliplatin

CSPC's argument that a POSA would have been motivated by the Conroy references to preemptively reduce FOLFIRINOX's 85 mg/m² oxaliplatin dose to the claimed dose of 60 mg/m² oxaliplatin relies on an improperly selective reading. *See, e.g.*, Paper 1 at 14-16, 41. "[I]n an obviousness analysis, prior art should be viewed *as a whole*." *Impax Lab'ys Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018) (emphasis added). Here, the Conroy references—read in their entirety—unambiguously teach initiation of FOLFIRINOX therapy at 85 mg/m² oxaliplatin, not the claimed 60 mg/m².

1. The Conroy References Define FOLFIRINOX as Including 85 mg/m² Oxaliplatin

The Conroy references define FOLFIRINOX as a regimen that comprises 85 mg/m² oxaliplatin. Conroy's abstract defines FOLFIRINOX as "oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks." Ex. 1003 at 1. As Conroy reports, patients in the FOLFIRINOX arm of the study received (1) 85 mg/m² oxaliplatin, followed by (2) 400 mg/m² leucovorin, (3) 180 mg/m² irinotecan, and (4) fluorouracil administered as a 400 mg/m² bolus dose followed by a 2400 mg/m² infusion. *Id.* at 3.

Conroy Protocol and Appendix likewise define FOLFIRINOX by reference to an 85 mg/m² starting dose of oxaliplatin. Conroy Protocol specifies that FOLFIRINOX treatment "will begin with oxaliplatin 85 mg/m² IV infused over 2 hours." Ex. 1004 at 15. Dr. Ratain does not dispute that Conroy Protocol teaches 85 mg/m² oxaliplatin as the starting dose. Ex. 2073 at 43:11-14, 83:11-18. A POSA reading Conroy in combination with Conroy Protocol and Conroy Appendix would understand that FOLFIRINOX refers to a treatment regimen defined by, *inter alia*, 85 mg/m² oxaliplatin. See Ex. 2076 ¶¶ 237-52.

Subsequent references, including those co-authored by Conroy himself, also define FOLFIRINOX as comprising 85 mg/m² oxaliplatin. Referring back to

Conroy, Conroy 2013 states that “[t]he FOLFIRINOX regimen included oxaliplatin (85 mg/m²) over 2 h, then irinotecan (180 mg/m²) over 90 min concurrently with leucovorin (400 mg/m²) over 2 h immediately following oxaliplatin, bolus 5-FU (400 mg/m²) and continuous intravenous infusion of 5-FU over 46 h (1,200 mg/m² per day for 2 days).” Ex. 1041 (Conroy 2013) at 2-3.

Other references refer to Conroy’s FOLFIRINOX as comprising 85 mg/m² oxaliplatin. *See, e.g.*, Ex. 2004 at 1-2 (“Promising phase II results with FOLFIRINOX (FFX) (oxaliplatin 85 mg/m² . . .) were confirmed in a sentinel phase III study (PRODIGE 4/ACCORD 11”); *see also* Ex. 2073 at 85:8-13, 97:21-98:4 (Dr. Ratain agreeing that other papers’ reference to FOLFIRINOX refers to a regimen comprising 85 mg/m² oxaliplatin). The fact that subsequent references that specifically describe the FOLFIRINOX regimen of Conroy as containing 85 mg/m² oxaliplatin directly contradicts CSPC’s urged interpretation otherwise.

CSPC ignores the significance of FOLFIRINOX’s 85 mg/m² dose of oxaliplatin. The 85 mg/m² dose is supported by study data and rationale. Specifically, Ychou et al., a reference that has several co-authors in common with Conroy, describes the results of a study aimed at determining the “recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors. Ex. 2038 (Ychou) at 1; *see also* Ex. 1003 at 2 (citing Ychou). Based on the results, which account for both

safety and efficacy, Ychou recommends “doses of 85 mg/m² for oxaliplatin.” Ex. 2038 at 7-8. A POSA would not readily set aside the 85 mg/m² dose, recommended by Ychou and employed in Conroy’s FOLFIRINOX. Ex. 2076 ¶¶ 152-60, 235-52.

CSPC also overlooks the significance of a starting, or “defined,” dose in the context of treatment. As Dr. Oberstein explains, the goal of treatment is to administer the most effective dose possible, up until the point that side effects become intolerable or otherwise compromise treatment. Ex. 2076 ¶¶ 50, 245. A POSA, understanding the significance of a starting dose, would not readily depart from the starting doses of FOLFIRINOX. Ex. 2076 ¶¶ 243-52.

2. Conroy’s Dose-Adjustment Protocol Would Not Have Motivated Preemptive Dose Reduction to 60 mg/m²

To the extent that Conroy refers to a dose of oxaliplatin lower than 85 mg/m², it is in the limited context of dose adjustment for some patients, in some instances of “predefined toxic events.” *See, e.g.*, Ex. 1003 at 3. Conroy Protocol and Conroy Appendix detail the conditions under which dose reduction might be appropriate. *See* Ex. 1004 at 15-20; Ex. 1017 at 3-9. At most, the Conroy references teach that toxicity events may prompt dose reduction *after* treatment

comprising oxaliplatin, 85 mg/m², has initiated and only for some patients, under certain circumstances.

Conroy Protocol and Appendix teach, if anything, that some toxicity events did not prompt oxaliplatin dose reduction, and some did. The majority of events prompt modifications *other than* oxaliplatin dose reduction. Ex. 2076 ¶¶ 154-57, 246-49; *see also id.* at ¶ 69. Dose reduction of irinotecan or 5-FU is generally recommended more frequently than oxaliplatin dose reduction. Ex. 2076 ¶¶ 154-57, 248-49; *see also id.* at ¶¶ 70-75. To the extent that some events prompted oxaliplatin dose reduction, they also prompted other modifications. *Id.*

Nor does Conroy's reported "median relative dose intensity" suggest or teach preemptive oxaliplatin dose reduction to 60 mg/m². *See* Paper 1 at 46-47. As Dr. Oberstein explains, Conroy's "median relative dose intensity" does not inform how many patients received dose reductions, or how many dose reductions occurred over the course of the study. Ex. 2076 ¶¶ 151-53, 241-42; Ex. 2073 at 84:9-12 (Dr. Ratain agreeing that the median relative dose intensity does not indicate the number of patients who were dose-reduced). Nor does it inform whether, or how many dose reductions of oxaliplatin occurred along with other modifications or connect study conclusions to a preemptively reduced dose of oxaliplatin. Ex. 2076 ¶¶ 151-53, 241-42. Rather, the conclusions of the study are based on a treatment regimen where all patients received at least an initial dose of

oxaliplatin, 85 mg/m². Ex. 2076 ¶¶ 149, 158-59, 245-48. This would not have motivated a POSA to pursue a first-line treatment regimen comprising 60 mg/m² oxaliplatin, let alone the claimed methods. Ex. 2076 ¶¶ 160, 250-52.²

Apart from the Conroy references, CSPC identifies no other basis for alleged motivation to modify FOLFIRINOX by preemptively reducing the dose of oxaliplatin to 60 mg/m². Rather, and consistent with Conroy Protocol and Conroy Appendix, the prior art reflects that oxaliplatin dose reduction was not the most frequently practiced modification to address toxicity concerns. *See* Ex. 2076 ¶¶ 253-61. For example, Mahaseth, Ginocchi, and Hatachi all cite Conroy and the toxicity issues observed with FOLFIRINOX. Ex. 1005 at 1; Ex. 1016 at 1; Ex. 1021 at 1, n.4. None identifies preemptive oxaliplatin dose reduction to address toxicity. Ex. 2076 ¶¶ 162-68, 210-12, 255-56. To the extent that certain of CSPC's references describe preemptive oxaliplatin dose reduction, it is not among the most frequently practiced modifications. Ex. 2076 ¶¶ 253-54, 257-58.

As a separate matter, CSPC identifies no motivation for a POSA to specifically pursue a 60 mg/m² dose of oxaliplatin. To the extent that CSPC's references disclose a starting oxaliplatin dose lower than 85 mg/m², they do not

² Gunturu describes a retrospective study of patients administered FOLFIRINOX, including data on dose modification. Gunturu reports that in practice the median average dose intensity of oxaliplatin was 90%, which is even further from the claimed 60 mg/m² oxaliplatin dose. *See* Ex. 2043 (Gunturu) at 3.

motivate a POSA to pursue 60 mg/m². *See* Ex. 2076 ¶¶ 257-61. Even if the prior art provided motivation to preemptively reduce the dose of oxaliplatin in FOLFIRINOX (it does not), a POSA would not be motivated to pursue 60 mg/m². Ex. 2076 ¶ 261.

C. General Toxicity Concerns Would Not Have Motivated the Multiple, Specific FOLFIRINOX Modifications Necessary to Arrive at the Invention

Despite repeatedly referring to FOLFIRINOX as the “gold standard” treatment for metastatic pancreatic cancer, CSPC argues that FOLFIRINOX nonetheless presented toxicity concerns that prompted its frequent modification. *See, e.g.*, Paper 1 at 16-17; Ex. 1002 at ¶ 234. On that basis, CSPC argues that a POSA would have been somehow motivated to arrive at the specific components and doses claimed by the ’552 patent.

Although CSPC’s references cite toxicity concerns, CSPC omits—and its expert did not consider—references that indicate, despite its toxicity, FOLFIRINOX was still a preferred treatment. For instance, the 2015 National Comprehensive Cancer Network (“NCCN”) Guidelines, a reference that Dr. Ratain did not consider³, identify FOLFIRINOX as a preferred category 1 recommendation for first-line treatment of metastatic pancreatic cancer. Ex. 2036 (NCCN Guidelines 2015) at 56. The NCCN Guidelines acknowledge toxicity

³ Ex. 2073 at 29:4-20.

concerns with FOLFIRINOX, but state that, “[d]espite the high levels of toxicity, no toxic deaths have been reported.” *Id.* at 56-57. Whether a POSA would have been motivated to modify FOLFIRINOX, which CSPC and Dr. Ratain repeatedly refer to as the “gold standard” in treatment, is questionable. *See* Ex. 2076 ¶¶ 55, 63.

Regardless, CSPC does not articulate how generalized concerns over toxicity would have motivated a POSA to make the four, specific modifications to FOLFIRINOX necessary to arrive at the ’552 patent’s claimed combination therapy. Indeed, the prior art reflects a number of different approaches for addressing toxicity concerns by modifying existing components of the FOLFIRINOX regimen without—as CSPC argues would have been obvious—introducing a new cytotoxic component, in a new dose. *See* Ex. 2076 ¶¶ 69-72, 262-69. Only by impermissible hindsight would a POSA, aware of all of these different approaches, arrive at the specifically claimed combination of drugs and doses. *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (“Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.”) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)).

A POSA would not have undertaken modifications to FOLFIRINOX lightly. *See* Ex. 2076 ¶¶ 262-69. Patients with metastatic pancreatic cancer are at an

advanced stage of the disease. *Id.* at ¶¶ 47-48, 263; *see also id.* at ¶¶ 49-55. As such, the goal of first-line therapy is to administer the most effective dose that a patient can tolerate. Ex. 2076 ¶¶ 50, 263. As dose reduction may compromise efficacy, a POSA would not undertake dose reduction without a strong rationale for doing so. *Id.* Consistent with this, the prior art reflects a variety of FOLFIRINOX modifications less extreme than what CSPC proposes, for example dose reduction of a single component (e.g., removal of the 5-FU bolus) or dose modification of existing components. Ex. 2076 ¶¶ 56-63, 253-64.

If motivated to modify FOLFIRINOX, a POSA would have been aware of a number of different approaches, e.g., modification to one or more existing FOLFIRINOX components. *See* Ex. 2076 ¶¶ 56-63, 262, 265. As Dr. Oberstein explains, against this backdrop, a POSA would not have been motivated to make all four of CSPC's allegedly obvious FOLFIRINOX modifications simultaneously. *Id.* at ¶¶ 228-36.

Indeed, the variety of modifications to FOLFIRINOX that addressed toxicity issues persisted after the '552 patent's effective filing date. *See* Ex. 2076 ¶ 266. That this variety persisted underscores the lack of clear direction—or motivation—in the prior art for one approach over another, much less the specific modifications that CSPC urges. Ex. 2076 ¶¶ 228-34, 266-69.

Dr. Ratain fails to identify motivation specific to CSPC's allegedly obvious FOLFIRINOX modifications. At his deposition, he testified generally:

Q: What are the proposed modifications to the FOLFIRINOX regimen that you believe were obvious to do?

A: Well, the two modifications are to make it work better and to make it less toxic. Those were the – the two goals of anybody modifying a regimen.

Ex. 2073 at 53:2-7; *see also id.* at 92:14-93:14 (testifying, generally, that “there’s always a reason to make things better, and there’s always concern about trying to make things better.”).

Such conclusory testimony is insufficient to establish obviousness and is “fraught with hindsight bias.” *See ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1327-28 (Fed. Cir. 2012) (expert testimony that “[t]he motivation to combine would be because you wanted to build something better” was conclusory and insufficient). As in *ActiveVideo Networks, Inc.*, Dr. Ratain’s testimony on the alleged motivation of a POSA “is generic and bears no relation to any specific combination of prior art elements.” *Id.* at 1328. Accordingly, it cannot support obviousness.

D. The Known Properties of Liposomal Irinotecan Would Not Have Motivated a POSA to Pursue the Claimed Methods

CSPC argues that—in addition to modifying existing FOLFIRINOX components—a POSA would have been further motivated to introduce an entirely

new component to the regimen, effectively creating a new combination therapy. *See, e.g.*, Paper 1 at 42-43. To the extent that CSPC articulates a POSA's alleged motivation in this regard, it cites the allegedly "superior" properties of liposomal irinotecan known at the time. But, as discussed below, a POSA would not have understood any allegedly superior properties of liposomal irinotecan to translate to a superior combination therapy.

1. Bayever, Ko, and/or Saif Do Not Motivate the Substitution of Liposomal Irinotecan Into Any Oxaliplatin-Containing Therapy, Let Alone FOLFIRINOX

At his deposition, Dr. Ratain admitted that liposomal irinotecan is a "distinct product" from irinotecan, with "different properties." Ex. 2073 at 49:7-12. Dr. Ratain moreover explained that the "different properties" of liposomal irinotecan do not, in his opinion, translate to a superior approach:

[W]hat's unclear is whether liposomal irinotecan can increase the efficacy of irinotecan. It's just not entirely clear. . . . [I]t's not yet been proven that this formulation or this schedule of giving irinotecan, so to speak, is superior than the more conventional, historical approach.

Id. at 50:23-51:19. Dr. Ratain confirmed that this was true as of August 21, 2015.

Id. at 51:20-24. Dr. Ratain's testimony undermines any alleged motivation based on properties of liposomal irinotecan known to a POSA.

As Dr. Oberstein explains, none of Dr. Ratain's cited references on the theoretical superiority of liposomal irinotecan suggest that its combination with

other of the '552 patent's claimed components—most notably, oxaliplatin—might translate to an improved therapy. *See* Ex. 2076 ¶¶ 270-81. Bayever, which is entirely silent on any combination therapy that includes oxaliplatin, would not motivate a POSA to combine liposomal irinotecan with any oxaliplatin-containing therapy, much less oxaliplatin in the claimed dose of 60 mg/m². Ex. 2076 ¶¶ 270, 274; *see also id.* at ¶¶ 169-80. Ko is likewise silent on any treatment regimen that comprises liposomal irinotecan and oxaliplatin and suggests, at most, the utility of liposomal irinotecan as monotherapy or in combination with gemcitabine. *See* Ex. 2076 ¶¶ 270-71; *see also id.* at ¶¶ 186-92. Saif is also silent on any combination therapy that includes oxaliplatin and liposomal irinotecan and provides no motivation to combine the two. Ex. 2076 ¶¶ 270, 272-73; *see also id.* at ¶¶ 181-85. If anything, a POSA would understand Saif to reflect recognition in the field that the combination of oxaliplatin and irinotecan present countervailing toxicity concerns. Ex. 2076 ¶¶ 272-73.

Indeed, a POSA would have been aware of the risk that a combination of irinotecan and oxaliplatin, two chemotoxic drugs, might present dose-limiting toxicity. *See* Ex. 2076 ¶¶ 277-81; Ex. 1054 at 6 (identifying neutropenia as a “severe irinotecan-associated toxicity”). A POSA would have been cautious, due to the risk of neutropenia, to substitute liposomal irinotecan into FOLFIRINOX. Ex. 2076 ¶¶ 277-81.

Dr. Ratain cites other references in support of a POSA's alleged motivation to substitute liposomal irinotecan into FOLFIRINOX. But as Dr. Oberstein explains, none of these references provide such motivation, much less motivation to substitute liposomal irinotecan in the '552 patent's specifically claimed dose of 60 mg/m². Ex. 2076 ¶¶ 275-76, 282-87. If anything, certain of Dr. Ratain's cited references underscore the difficulty in arriving at the specifically claimed dose. And, as Dr. Ratain testified at his deposition, "none of these drugs were ever optimized, the dosages. Nobody really knows what – you know, whether more is better is the real issue." Ex. 2073 at 77:9-15.

None of Dr. Ratain's references even purport to correlate the dose of irinotecan in FOLFIRINOX to a hypothetical dose of liposomal irinotecan in FOLFIRINOX. To the contrary, certain references suggest the difficulty a POSA might face in attempting to make such correlation. The '209 application (Ex. 1015) explicitly states, for instance, that such "quantitative comparisons are difficult" between irinotecan and liposomal irinotecan. *See* Ex. 1015 at 52 ("The comparison is qualitative, as both irinotecan and nal-IRI have been used in different doses and schedules as monotherapy and combination therapy with other chemotherapeutic agents; therefore quantitative comparisons are difficult.").

2. CSPC Identifies No Motivation to Substitute Liposomal Irinotecan Into a FOLFIRINOX Regimen That Also Includes 60 mg/m² Oxaliplatin and Omits a 5-FU Bolus

As discussed, a variety of modifications to existing components of FOLFIRINOX were known to a POSA, none of which entailed switching one cytotoxic component for another, and in a different dose. A POSA would not have been motivated, in light of the variety of modifications already known to address the issue, to further modify FOLFIRINOX by introducing a new component to the regime. Ex. 2076 ¶¶ 233-34, 276, 281.

CSPC's and Dr. Ratain's cited references provide no such motivation. As discussed, Saif explicitly questions the value of substituting liposomal irinotecan into FOLFIRINOX, given countervailing toxicity concerns. Ex. 1007 at 1. Even so, nothing in Saif suggests substituting liposomal irinotecan into a modified regimen, specifically one that includes 60 mg/m² oxaliplatin and no 5-FU bolus. *Id.* Ko suggests, if anything, liposomal irinotecan as monotherapy, not as a substitution in FOLFIRINOX. Ex. 1008 at 1, 5. And Bayever discloses liposomal irinotecan in a regimen that—unlike FOLFIRINOX—lacks oxaliplatin, in any dose. *See generally* Ex. 1006.

Even if a POSA were somehow motivated by its allegedly superior properties, CSPC does not articulate why a POSA would be motivated to introduce liposomal irinotecan to a modified FOLFIRINOX regimen over FOLFIRINOX. And, even if motivated to introduce liposomal irinotecan to a modified FOLFIRINOX regimen, a POSA would have had a variety of options from which

to choose. *See* Ex. 2076 ¶ 59. As discussed, there were a number of modified FOLFIRINOX regimens that did not include an oxaliplatin dose reduction and 5-FU bolus removal. *See supra*; *see also* Ex. 2076 ¶¶ 56-63, 262-65. CSPC articulates no motivation to substitute liposomal irinotecan into a modified FOLFIRINOX regimen that comprises oxaliplatin dose reduction to 60 mg/m² and omission of the 5-FU bolus over numerous other options.

3. The Prior Art as a Whole Does Not Motivate the Claimed Dose of Liposomal Irinotecan

CSPC's petition does not articulate specific motivation to—in addition to the other allegedly obvious FOLFIRINOX modifications—use the claimed amount of 60 mg/m² liposomal irinotecan as a substitute for the 180 mg/m² irinotecan in FOLFIRINOX. To the extent that Dr. Ratain identifies any such motivation, it is based on Bayever's alleged disclosure that liposomal irinotecan in the range of 60-80 mg/m² was “tolerable in most patients.” *See* Ex. 1002 at ¶¶ 239-40. But the prior art as a whole does not motivate the specifically claimed 60 mg/m² dose of liposomal irinotecan.

Dr. Ratain and CSPC ignore other references that teach doses of liposomal irinotecan that are higher than the claimed 60 mg/m² dose. As Dr. Oberstein explains, these references disclose doses of liposomal irinotecan that are 120 mg/m² every three weeks, which is a higher weekly dose than claimed. Ex. 2076

¶ 285. Neither CSPC nor Dr. Ratain attempts to explain why a POSA would have ignored other references in favor of Bayever.

To the extent that CSPC and Dr. Ratain rely solely on Bayever by reason of its common inventorship with the '552 patent inventors, that is improper hindsight. CSPC's petition notes that Bayever is the "Patent Owner's prior published patent application," and Dr. Ratain notes that two of Bayever's named inventors are "the same named inventors of the '552 patent." Paper 1 at 2; Ex. 1002 at ¶ 114. That Bayever shares some identity with the '552 patent's inventors is irrelevant to obviousness. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."); 35 U.S.C. § 103; *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."). "What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm.*, 678 F.3d at 1296. CSPC's and Dr. Ratain's overreliance on Bayever for motivation to select the claimed 60 mg/m² dose of liposomal irinotecan, to the extent it is based on identity of inventorship, is improper.

E. CSPC Fails to Show That a POSA Would Reasonably Expect That Its Multiple, Specific FOLFIRINOX Modifications Would Achieve the Claimed Invention

CSPC fails to show that a POSA would have been motivated to make the multiple, specific modifications to FOLFIRINOX that would result in the '552 patent's claimed therapy. CSPC's obviousness challenge fails for that reason alone. Separately, CSPC also fails to show that—even if so motivated—a POSA would reasonably expect that CSPC's multiple urged modifications to FOLFIRINOX would result in the claimed methods.

1. CSPC Improperly Relies on the Outcomes Reported for Prior-Art Regimens

The obviousness inquiry looks at differences between the prior art and the “claimed invention.” *See* 35 U.S.C. § 103. Accordingly, “[t]he reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of *the claimed invention*.” *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (emphasis added).⁴

CSPC improperly relies on outcomes reported for prior-art regimens to evidence a POSA's expectations with regard to the claimed multi-drug regimen.

⁴ *See also Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 141 F.4th 1367, 1379 (Fed. Cir. 2025) (“It is bedrock law that the inquiry of motivation and reasonable expectation of success must focus on arriving at the *claimed invention*.”) (emphasis in original).

CSPC cites portions of Dr. Ratain's declaration as discussing the "expected results" of lower doses of chemotherapy drugs, for instance. *See* Paper 1 at 51 (citing Ex. 1002 at ¶¶ 253-62). In the cited portions, Dr. Ratain simply restates the same teachings from each reference that allegedly support motivation to combine. *See* Ex. 1002 at ¶¶ 253-62 (discussing the Conroy references, Mahaseth, Bayever, Saif, and Ko). But whether a POSA would reasonably expect "the prior art references to operate as those references intended" is not the correct inquiry. *See Intelligent Bio-Systems, Inc.*, 821 F.3d at 1367. CSPC and Dr. Ratain cannot rely on prior-art outcomes as indicative of a reasonable expectation of success in the claimed invention.

Indeed, the outcomes reported for Dr. Ratain's cited references are for treatment regimens different from the claimed invention. Dr. Ratain opines that a POSA would have expected success at 60 mg/m² oxaliplatin, because the Conroy references teach 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." Ex. 1002 at ¶ 242. But Dr. Ratain ignores, as discussed *supra*, that the clinical outcomes of Conroy are for a regimen that employs, among other differences, a starting dose of 85 mg/m² oxaliplatin and does not include liposomal irinotecan.

Dr. Ratain opines that a POSA would have pursued a 60 mg/m² dose of oxaliplatin, because “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 cancer patients.” Ex. 1002 at ¶ 242. But Dr. Ratain ignores that Cantore is silent on any treatment that includes—as the claimed methods do—liposomal irinotecan, 5-FU, or LV, at any dose(s). *See* Ex. 2076 ¶ 260; *see also id.* at ¶¶ 78, 193-200.

Dr. Ratain opines that a POSA would have known, based on Mahaseth, “that a modification of the 5-FU dose would also improve the toxicity profile.” Ex. 1002 at ¶ 244. But, as discussed, Mahaseth does not include liposomal irinotecan, at any dose, or oxaliplatin at the claimed dose. *See supra* Section VI.F.

Dr. Ratain opines, “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.” Ex. 1002 at ¶ 261 (also citing Saif and Ko). But Bayever describes three-drug treatment regimens that—unlike the claimed four-drug combination therapy—do not include oxaliplatin in any dose. *See supra* Section VI.C. Saif reports outcomes of the second-line, three-drug NAPOLI-1 regimen, and Ko reports the results of the second-line, single-drug liposomal irinotecan monotherapy. *See supra* Section VI.D-E. Thus, Dr. Ratain’s statement that a “POSA would also know that the combination disclosed in Bayever had been

successful as based on Saif” (Ex. 1002 at ¶ 238) does not inform any expectations regarding the ’552 patent’s claimed first-line, four-drug combination therapy.

2. CSPC’s Alleged “Reasonable Expectation of Success” Relies on an Erroneous Claim Construction

To the extent that CSPC otherwise purports to address the “reasonable expectation of success” prong of the obviousness inquiry, it is through an erroneous claim-construction argument. Specifically, CSPC argues that “treating” and “treat” should be understood to mean “attempting to cause a therapeutic improvement but not requiring actual efficacy.” *See* Paper 1 at 26-27. Under such construction, CSPC argues that “the POSA would only need to combine the prior art to arrive at a first-line treatment regimen administered *for the purpose of treating metastatic pancreatic cancer*, and not with the expectation that the regimen would have superior clinical efficacy.” Paper 1 at 49-50; *see also id.* at 27 (equating the claimed methods of treatment to methods of administering the recited components in the recited doses, at the recited frequency, to the recited patient population). CSPC’s claim-construction argument improperly seeks to obviate proof of “reasonable expectation of success.”

CSPC is incorrect that the claims require no more than administration of the claimed combination. *See supra* Section IV. And a construction that the claimed treatments provide more than a *de minimis* benefit finds support in the priority application. *See supra id.*

Indeed, the Board rejected CSPC's argument that, here, treatment requires only administration of the claimed combination. Specifically, the Board found that "the ordinary understanding of a claim reciting a 'method of treating metastatic adenocarcinoma of the pancreas' that comprises 'administering an antineoplastic therapy to the patient' in order 'to treat the metastatic adenocarcinoma of the pancreas' is that the 'treatment' would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated." Paper 13 at 14. In light of the Board's finding, a "reasonable expectation of success" here is whether a POSA would reasonably expect CSPC's urged FOLFIRINOX modifications to provide more than a *de minimis* therapeutic benefit or efficacy. CSPC's arguments predicated on an understanding of "treatment" that requires no more than administration fail.

3. CSPC's "Result-Effective Variable" Argument Fails, Again

To the extent that CSPC purports to articulate any other basis for a "reasonable expectation of success," it is that oxaliplatin dose reduction is a "result-effective" variable. *See* Paper 1 at 46-47. Specifically, CSPC argues that "lowering the dose of oxaliplatin from 85 mg/m² in FOLFIRINOX to the claimed 60 mg/m² would have been routine optimization." *Id.* CSPC's argument is without merit.

As an initial matter, a POSA would not consider dose adjustment in this context to be a matter of “routine experimentation.” Ex. 2076 ¶¶ 80-89, 291-93; *see also id.* at ¶¶ 76-79. And the question of whether oxaliplatin is a result-effective variable has already been decided in favor of patentability. As CSPC itself asserts, “the Office steadfastly maintained throughout prosecution that lowering the dose of oxaliplatin from 85 mg/m² in FOLFIRINOX to the claimed 60 mg/m² was a ‘result effective variable’ that rendered the claims obvious.” *See* Paper 1 at 46. Ipsen overcame these arguments during prosecution, and CSPC articulates no basis to revisit the issue.

Separately, CSPC’s “result-effective variable” argument ignores that oxaliplatin dosage is not the only difference between FOLFIRINOX and the claimed regimen. Rather, each regimen comprises a combination of *four separate drugs*, each in its own specific dosage. *See* Ex. 1001 at claim 1; Ex. 1003 at 3. The four drugs in the ’552 patent’s claimed combination therapy had never been administered in combination, making it an entirely new combination therapy. That combination therapies existed at the time of invention does not render the ’552 patent’s novel, four-drug combination therapy obvious. *See, e.g.*, Ex. 2076 ¶¶ 76-79.

Oxaliplatin dose reduction is not a “result-effective variable” where, as here, the invention comprises multiple components that may interact in unpredictable

ways. The Federal Circuit has recognized that “in cases with multiple result-effective variables, ‘[e]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious.’” *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376 (Fed. Cir. 2021) (citation omitted). As Dr. Oberstein explains, such evidence is present here, where the drugs at issue and inter-patient variability render the clinical effect of multiple changes to a combination therapy unpredictable. Ex. 2076 ¶¶ 288-93. For these reasons, CSPC’s “result-effective variable” argument fails.

4. CSPC’s Cited Data Would Not Have Inspired a Reasonable Expectation of Success in the Claimed Treatment

A POSA would understand that the effect of CSPC’s multiple, specific modifications to FOLFIRINOX is tantamount to an entirely new combination therapy, composed of different components in different doses. Ex. 2076 ¶¶ 294-300; *see also id.* at ¶¶ 100-19. And as Dr. Oberstein explains, a POSA would be aware that, in developing new treatments for metastatic pancreatic cancer, the likelihood of successful new combination therapies is particularly low. *Id.* at ¶¶ 90-99, 295-302.

CSPC relies on the preclinical data reported in Bayever (and other references) and early-stage clinical data regarding liposomal irinotecan to support a reasonable expectation of success in practicing the claimed therapies. *See, e.g.*, Paper 1 at 8 (citing “pre-clinical and pharmacological properties”); Ex. 1002 at ¶

238. This data, even if known to a POSA, would not support any reasonable expectation of success in a combination therapy that provides more than a *de minimis* benefit absent comparative testing. *See* Ex. 2073 at 108:3-23.

As Dr. Oberstein explains, preclinical data regarding liposomal irinotecan, by itself, would not have inspired a reasonable expectation of success in practicing the claimed, four-drug combination therapy. Ex. 2076 ¶¶ 92-94, 275-76, 300-01. Further, and as evidenced by Dr. Ratain's own publications, a POSA would have understood that the early-phase clinical data that CSPC cites is not necessarily predictive of successful clinical outcomes, much less for a new combination therapy composed of different drugs. *See id.* at ¶¶ 95-99, 295-302.

5. CSPC Ignores Unpredictability of Clinical Effects at Different Doses in Combination Therapy

As discussed *supra*, CSPC ignores that the prior art as a whole does not motivate the claimed 60 mg/m² dose of liposomal irinotecan, alone or in combination with other components. CSPC further ignores the unpredictability of clinical effects of the drugs at issue, particularly in combination.

As Dr. Oberstein explains, oncology drugs have a narrow therapeutic index and inter-individual pharmacokinetic variability, which results in “unpredictable clinical effects.” Ex. 2076 ¶ 292. This unpredictability is compounded in the context of combination therapy, involving more than one oncology drug. Ex. 2076 ¶ 300; *see also* Ex. 2073 at 62:12-63:15 (describing the “infinite number of

possibilities” a POSA might face in assessing the maximum dose for a combination therapy). The drugs at issue are associated with significant pharmacokinetic variability. Ex. 2076 ¶¶ 292-93. Moreover, the non-linear pharmacokinetics of certain of the drugs at issue further frustrates the ability to predict clinical effect. Ex. 2076 ¶ 292.

CSPC fails to account for this unpredictability, which—even if a POSA were motivated to pursue 60 mg/m² liposomal irinotecan—undermines any reasonable expectation of success at that dose, especially in combination with other components. Dr. Ratain opines that Saif and Ko offer, at most, “hope[] of improving the overall survival of patients with pancreatic cancer.” Ex. 1002 at ¶ 261. But as the Federal Circuit has recognized, “hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this.” *OSI Pharms., LLC v. Apotex, Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). Here, as in *OSI Pharms.*, CSPC fails to establish a reasonable expectation of success in this unpredictable field.

F. Unexpected Results Properly Support Non-Obviousness

Unexpected results may support a finding of non-obviousness where they reflect a difference in kind, not just in degree, from the prior art. *Allergan v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015). The Federal Circuit has found

that a difference in kind may constitute, e.g., “the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment.” *See id.* at 1307.

Nichetti and Nevala-Plagemann do not establish “identical or clinically insignificant efficacy differences” between FOLFIRINOX and the claimed methods. *See* Ex. 1002 at ¶ 260. As Dr. Oberstein explains, to the extent that the findings of Nichetti suggest comparative efficacy between NALIRIFOX and FOLFIRINOX, they also indicate differences in toxicity. *See* Ex. 2076 ¶¶ 218-21, 311-12. Further, a POSA would understand that the reported improvements, while maintaining efficacy, represent a fundamental therapeutic advance, not an expected, incremental change. *Id.* at ¶ 310. At most, Nevala-Plagemann purports to identify issues for future consideration and study. *See id.* at 2 (concluding that further research is needed to assess the benefit of NALIRIFOX over existing treatment options); *see also* Ex. 2076 ¶¶ 222-25.

CSPC argues that any clinical benefit conferred by the claimed methods was not “unexpected,” because Bayever allegedly teaches that liposomal irinotecan is “superior” to free irinotecan, and a POSA would have therefore expected the claimed regimen to be superior to FOLFIRINOX. *See* Paper 1 at 34; Ex. 1002 at ¶ 261. Dr. Ratain relies on the same references that allegedly motivate substitution of liposomal irinotecan for free irinotecan to argue that clinical benefits of the

claimed regimen were not unexpected. *See* Ex. 1002 ¶ 261. Motivation, however, is no substitute for an explanation of why the benefits of the claimed regimen were not unexpected. By reiterating the same arguments used for motivation, CSPC ignores whether a POSA would have had a reasonable expectation of success in arriving at the claimed methods. As discussed *supra*, a POSA would not have. CSPC's argument against unexpected results is deficient.

Comparable efficacy and improved toxicity profile relative to FOLFIRINOX is a difference in kind, particularly given the extent of differences between the two regimens. As discussed, the claimed methods differ from FOLFIRINOX by (1) 5-FU bolus removal; (2) oxaliplatin dose reduction; and (3) inclusion of liposomal irinotecan (4) in a dose of 60 mg/m². In summary, the differences entail two dose reductions and introduction of a new component. A POSA would understand that dose reduction of multiple components in a combination therapy may, as a general matter compromise efficacy. Ex. 2076 ¶¶ 263, 306-08; *see also id.* at ¶¶ 288-91. That the claimed methods provide comparable efficacy with an improved toxicity profile was unexpected. *Id.* at ¶¶ 303-309.

Improved efficacy (measured by prolonged survival) with an improved toxicity profile constitutes a "difference in kind." As Dr. Oberstein explains, the challenge of treatment is to administer the most effective regimen while avoiding toxicity issues that may require discontinuation of treatment or otherwise

compromise efficacy of the most effective dose. Ex. 2076 ¶ 307; *see also id.* at ¶¶ 310-12. And in this field, an improvement overall by weeks can be significant. Post-priority references suggest that NALIRIFOX offers improved efficacy and tolerability over gemcitabine/nab-paclitaxel, while FOLFIRINOX did not. *Id.* at ¶ 309. As Dr. Oberstein explains, the available data indicates that the '552 patent's claimed methods offer a difference in kind over existing pancreatic cancer treatments. *Id.* at ¶¶ 303-309.

IX. GROUND 2: CPSC FAILS TO SHOW THAT CLAIMS 2, 7, AND 15 ARE OBVIOUS IN VIEW OF MASI AND GINOCCHI, ALONE OR IN COMBINATION WITH CPSC'S OTHER ASSERTED REFERENCES

There is no dispute that none of CSPC's asserted references recite—as required by claim 2—that oxaliplatin is administered 2 hours after liposomal irinotecan. *See* Paper 1 at 59. And CSPC's obviousness challenge of claim 2 is entirely unsupported by expert testimony. Ex. 2073 at 22:12-20 (Dr. Ratain admitting that he does not opine on claim 2)⁵; Ex. 2076 ¶ 315. CSPC's obviousness challenge to claim 2 consists of attorney argument.

Further, there is no dispute that each of claims 2, 7, and 15 recite, *inter alia*, that administration of liposomal irinotecan precedes that of oxaliplatin. None of

⁵ Nor does Dr. Ratain discuss Masi or Ginocchi in connection with CSPC's Ground 2. *See* Ex. 1002 at ¶¶ 308-311.

CSPC's references, alone or in combination, suggest any sequence of administration where liposomal irinotecan is administered before oxaliplatin.

Significantly, CSPC's lead reference teaches the opposite sequence of administration as recited in the '552 patent's claims 2, 7, and 15. Conroy states that "FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector." Ex. 1003 at 3. A POSA would understand, based on this disclosure, to administer oxaliplatin prior to at least irinotecan. Ex. 2076 ¶¶ 317-22. CSPC simply ignores this teaching in the art.

Bayever does not teach the recited sequences, because—as discussed *supra*—it is silent on a combination therapy that includes liposomal irinotecan and oxaliplatin, let alone administered in any particular sequence. CSPC relies on Bayever's alleged disclosure that "liposomal irinotecan MM-398 should be administered first before any other drugs." Paper 1 at 58. The only citation to Bayever that CSPC provides in this respect is to claim 4, which recites, "The method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU." Ex.

1006 at 54 (claim 4). A POSA would not understand Bayever to teach any of the recited sequences of administration. Ex. 2076 ¶¶ 315-23; *see also id.* at ¶¶ 169-80.

A POSA would not understand Masi to teach the recited sequences. Masi relates to treatment of an entirely different type of cancer, namely metastatic colorectal cancer. Ex. 1012 at 1. A POSA would not readily apply the teachings of Masi to the claimed patient population. Ex. 2076 ¶ 324; *see also id.* at ¶¶ 201-09. Moreover, Masi appears to predate Conroy and the emergence of FOLFIRINOX as the first-line standard of treatment of metastatic pancreatic cancer by over six years. *Compare id.* at 1 (“accepted 12 July 2004”) *with* Ex. 1003 at 1 (bearing a publication date of May 12, 2011). And as discussed, Conroy discloses—opposite to the claimed sequences—administration of oxaliplatin before irinotecan. *See* Ex. 1003 at 3. A POSA would not consider the teachings of Masi over those of Conroy in considering the sequence of administration of components in combination therapy for the treatment of metastatic pancreatic cancer. Ex. 2076 ¶¶ 325-27.

A POSA would not understand Ginocchi, which is silent on sequence of administration, to teach the recited sequences. As with Masi, Ginocchi does not disclose a treatment regimen that includes liposomal irinotecan, in any dose or administered in any sequence. At most, Ginocchi states that “[t]he regimen included a lower dose of irinotecan (administered at 150 mg/sqm on day 1 every

14 days) and of infusional 5-fluorouracil (2800 mg/sqm administered as a 48-hour continuous infusion on days 1 to 3 every 14 days). Folinic acid and oxaliplatin remained unchanged.” Ex. 1016 at 1. If anything Ginocchi indicates—as discussed *supra*—that a POSA would have been aware of modifications to FOLFIRINOX capable of addressing toxicity concerns. Ex. 2076 ¶¶ 210-13, 328-31.

CSPC argues that claim 7—which requires administration of each of the four recited drugs in a particular order—is obvious for essentially the same reasons as presented for claims 1 and 2. *See* Paper 1 at 59. CSPC additionally cites “the fact that Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen with leucovorin immediately preceding it and that Bayever also discloses that 5-FU is administered last with leucovorin immediately preceding it.” *Id.* CSPC ignores that, contrary to the recited sequence of claim 7, both Conroy and Mahaseth describe administration of oxaliplatin prior to irinotecan. *See* Ex. 1003 at 3; Ex. 1005 at 2. CSPC’s arguments otherwise fail for the same reasons discussed with respect to claims 1 and 2.

None of CSPC’s cited references disclose a treatment regimen that comprises the four recited drugs, much less in the order of administration recited by claim 7. Conroy (Ex. 1003) and Mahaseth (Ex. 1005) do not contain any teaching, suggestion, or motivation with respect to a combination therapy that

includes liposomal irinotecan, much less the order in which liposomal irinotecan is administered with other drugs. To the extent that Bayever discusses an order of administration, it is in the context of a three-drug combination therapy that does not include—as the ’552 patent claimed therapy does—oxaliplatin. A POSA would not be motivated based on these references to pursue the claimed combination therapies, in the recited order of administration. Ex. 2076 ¶¶ 332-346.

CSPC argues that claim 15—which requires administration of the recited drugs in an order and also comprises administration of a corticosteroid and an antiemetic prior to antineoplastic therapy—is obvious for essentially the same reasons as presented for claims 1 and 2 and in further view of Bayever. CSPC relies on Bayever’s alleged disclosure of administration of dexamethasone, which is a corticosteroid, and an anti-emetic prior to antineoplastic therapy. *See* Paper 1 at 60. CSPC also cites conclusory testimony by Dr. Ratain that such administration was “known to a POSA” and “standard medical practice.” *See* Ex. 1002 at ¶¶ 310-11. Dr. Oberstein disagrees with Dr. Ratain’s conclusory statements. *See* Ex. 2076 ¶¶ 347-52. CSPC’s argument also fails for the reasons already discussed with respect to Ground 1.

X. GROUND 3: CSPC FAILS TO SHOW THAT CLAIMS 1-15 ARE OBVIOUS IN FURTHER VIEW OF CARNEVALE AND DEAN

CSPC presents an alternate theory of obviousness that is premised on an effective date of November 10, 2017, citing Carnevale (Ex. 1013) and Dean (Ex.

1014) in addition to the same arguments presented for grounds 1 and 2 as allegedly invalidating. Paper 1 at 60-63. CSPC’s alternate theory fails for at least the reason that, as discussed *supra*, the ’552 patent properly claims an effective filing date of August 21, 2015. Carnevale and Dean are not prior art, and CSPC’s arguments fail for the reasons discussed with respect to Grounds 1 and 2. Regardless, CSPC’s alternate theory of obviousness fails as discussed below.

As an initial matter, CSPC identifies no intrinsic support for a claim construction that requires some (unspecified) degree of clinical efficacy.⁶ At most, CSPC suggests that the ’552 patent applicant’s arguments during prosecution support such requirement. *See* Paper 1 at 35 (“[T]he Patent Owner argued that the Challenged Claims are ***directed to clinical efficacy*** in a human suffering from metastatic pancreatic cancer.” (citing Ex. 1119 at 153) (emphasis added)). But the cited portion appears in February 25, 2022 remarks, under the heading, “Unexpected Results.” *See* Ex. 1119 at 151-53. In this section, Ipsen does not argue—as CSPC alleges—that the claims are “directed to clinical efficacy.” Rather, and as discussed *supra*, Ipsen submitted that the claimed therapy has “unexpected therapeutic effects.” Ex. 1119 at 153. This does not equate to a claim requirement of clinical efficacy.

⁶ The Board found in its Institution Decision that the ’552 patent claims do not require clinical efficacy. Paper 13 at 45.

Regardless, CSPC’s asserted references do not support obviousness, because they do not even purport to describe “clinical efficacy” of the ’552 patent’s claimed therapies. At most, Carnevale restates the results of the study described in Ko (Ex. 1008), an early-stage study of liposomal irinotecan as a monotherapy, and the study referenced in Saif (Ex. 1007), a study of a three-drug combination therapy that does not include oxaliplatin. *See* Ex. 1013 at 7 (restating Ko), 8 (restating Saif); *see also* Ex. 2076 ¶¶ 214-16, 353-61. Dean similarly lacks any description of the specifically claimed therapies, much less their “clinical efficacy.” *See* Ex. 1014; *see also* Ex. 2076 ¶¶ 217-18, 362-64. As Dr. Oberstein explains, neither reference bridges the gap between the prior art and the claimed invention, nor would a POSA reasonably expect to practice the claimed therapy based on their disclosures. Ex. 2076 ¶¶ 353-68.

If anything, Carnevale echoes that “progress in the therapeutic development of this disease has historically taken a slow and painstaking course, ***littered with numerous negative trial results.***” Ex. 1013 at 1 (emphasis added); *see also, e.g.*, Ex. 2012 at 1 (“[O]ncology drugs have the highest failure rates among the various therapeutic areas.”). Carnevale further characterizes pre-2010 efforts as a “stretch of failed or clinically inconsequential trials.” Ex. 1013 at 2. Carnevale’s characterization is consistent with a POSA’s particularly low expectations of success in the relevant field and endeavor, further supporting non-obviousness of

the '552 patent's claimed methods. *See supra* at Section VIII.D; *see also* Ex. 2076 ¶¶ 361, 364-68.

XI. CONCLUSION

Patent Owner respectfully submits that Petitioner has not carried its burden and that patentability of the challenged claims should be confirmed.

Date: November 10, 2025

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CERTIFICATE OF LENGTH (37 C.F.R. § 42.24(D))

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 13,507 words and thus complies with the applicable word limit.

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(E))

The undersigned hereby certifies that on November 10, 2025 copies of the foregoing document and supporting exhibits were served upon the following parties via electronic mail, with a copy to ipdocket@foxrothschild.com (referencing Attorney Docket No. 340008.00021):

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