

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

IPR2025-00505¹
Patent 11,344,552 B2

Before ZHENYU YANG, TAWEN CHANG, and TIMOTHY G. MAJORS,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

¹ Apotex Inc., which filed a petition in IPR2025-01531, has been joined as a petitioner in this proceeding.

JUDGMENT
Final Written Decision
Determining Some Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Granting Petitioner’s Motion to Seal (Paper 31)
37 C.F.R. §§ 42.14, 42.54

Denying Petitioner’s Motion to Exclude (Paper 43)
37 C.F.R. § 42.64(c)

Denying Patent Owner’s Motion to Exclude (Paper 42)
37 C.F.R. § 42.64(c)

I. INTRODUCTION

CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, “Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking *inter partes* review of claims 1–15 of U.S. Patent No. 11,344,552 B2 (Ex. 1001, “the ’552 patent”). Ipsen Biopharm Ltd. (“Patent Owner”) filed a Preliminary Response. Paper 9 (“Prelim. Resp.”). We instituted trial to review the challenged claims (Paper 13, “DI”).

Thereafter, Patent Owner filed a Response to the Petition (Paper 21, “PO Resp.”), Petitioner filed a Reply to Patent Owner’s Response (Paper 32,² “Reply”), and Patent Owner filed a Sur-reply to Petitioner’s Reply (Paper 38, “Sur-reply”). Both parties also moved to exclude certain exhibits. Papers 42–45, 47, 48. An oral hearing for this proceeding was held

² Paper 32 was filed under seal. Petitioner also filed a redacted version of the Reply. *See* Paper 33.

on May 19, 2026, and the transcript of that hearing is of record. *See* Paper 52. At the panel’s request (Paper 49), each party also filed a post-hearing supplemental brief on certain issues relating to claim construction (Papers 50, 51).

The Board has jurisdiction under 35 U.S.C. § 6 and issues this Final Written Decision pursuant to 35 U.S.C. § 318 and 37 C.F.R. § 42.73. For the reasons provided below, we find Petitioner has shown, by a preponderance of the evidence, the unpatentability of claims 1, 3–6, and 8–14. Petitioner, however, has not shown, by a preponderance of the evidence, the unpatentability of claims 2, 7, and 15.

A. Related Matters

Petitioner identifies U.S. Patent Application No. 19/188,672 (“the ’672 application”), filed on April 24, 2025, as a related matter. Paper 22, 1. Petitioner represents that the ’672 application claims priority to the application that issued as the ’552 patent.

B. The ’552 Patent and Background Technology

The ’552 patent “relates to novel therapies useful in the treatment of pancreatic cancer, including the use of liposomal irinotecan in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer.” Ex. 1001, 1:21–25.

Pancreatic cancer is the fourth leading cause of cancer death in the United States. Ex. 1001, 1:29–31. It has an extremely poor prognosis, with the 5-year survival rate at 6%. *Id.* at 1: 30–32. The ’552 patent explains that FOLFIRINOX, the prior art combination chemotherapy of 5-fluorouracil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin, has been the standard of care for first-line treatment of metastatic pancreatic cancer. *Id.* at 1:50–54.

One dose regimen of FOLFIRINOX is 85 mg/m² oxaliplatin, 180 mg/m² irinotecan, and fluorouracil at a dose of 400 mg/m² administered by IV bolus followed by a continuous infusion of 2400 mg/m². *Id.* at 1:67–2:3. The FOLFIRINOX regimen has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011. *Id.* at 1:62–65.

According to the '552 patent, however, FOLFIRINOX, was known to have significant toxicity, and its use was limited to patients with better performance status. Ex. 1001, 1:55–56. “With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity.” *Id.* at 1:57–59. Other modified FOLFIRINOX regimens include, for example, elimination of the 5-FU bolus. *Id.* at 2:4–5.

Another known treatment for pancreatic cancer involves administration of MM-398. “MM-398 is a liposomal irinotecan and is marketed in the U.S. as the FDA-approved product ONIVYDE® in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.” Ex. 1001, 2:8–13.

The '552 patent discloses antineoplastic therapies for the treatment of pancreatic cancer, comprising the administration of liposomal irinotecan in combination with oxaliplatin and 5-FU to patients with previously untreated pancreatic cancer. Ex. 1001, 2:17–20. The 5-FU can be administered in combination with leucovorin. *Id.* at 2:22–23. The regimen with liposomal irinotecan, 5-FU, leucovorin, and oxaliplatin is known as NALIRIFOX. Pet. 51–52; PO Resp. 6; Ex. 1011, 1; Ex. 2032, 2.

According to the '552 patent, its antineoplastic therapies “can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens.” *Id.* at 2:23–25.

C. Illustrative Claim

Independent claim 1 is illustrative of the claimed subject matter and is reproduced below.

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, 46:64–47:9.

Independent claim 12 is similar to claim 1, except it requires “a human patient who has not previously received gemcitabine.” Ex. 1001, 48:7–19.

D. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Reference	Basis	Claims Challenged
Conroy, ³ Conroy Protocol, ⁴ Conroy Appendix, ⁵ Mahaseth, ⁶ Bayever, ⁷ Saif, ⁸ Ko, ⁹ Cantore ¹⁰	§ 103	1, 3–6, 8–14

³ Conroy, et al., *FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer*, 364 N. Engl. J. Med. 1817–25 (2011) (Ex. 1003, “Conroy”).

⁴ Certified English Translation of the Protocol of Conroy, et al, <https://www.nejm.org/doi/full/10.1056/NEJMoa1011923#APPNEJMoa1011923PRO> (2011) (Ex. 1004, “Conroy Protocol”).

⁵ Conroy Supplementary Appendix, 364 N. Engl. J. Med. (2011) (Ex. 1017, “Conroy Appendix”).

⁶ Mahaseth et al., *Modified FOLFIRINOX Regimen with Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma*, 42 Pancreas 1311–15 (2013) (Ex. 1005, “Mahaseth”).

⁷ Bayever et al., WO 2013/188586 A1, published Dec. 19, 2013 (Ex. 1006, “Bayever”).

⁸ Saif, *MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastatic Pancreatic Cancer*, 15 J. Pancreas 278–79 (2014) (Ex. 1007, “Saif”).

⁹ Ko, et al., *A multinational phase 2 study of nanoliposomal irinotecan sucrosfate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer*, 109 Br. J. of Cancer 920–25 (2013) (Ex. 1008, “Ko”).

¹⁰ Cantore, et al., *Combined Irinotecan and Oxaliplatin in Patients with Advanced Pre-Treated Pancreatic Cancer*, 67 Oncol. 93–97 (2004) (Ex. 1009, “Cantore”).

Reference	Basis	Claims Challenged
Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, ¹¹ Ginocchi ¹²	§ 103	2, 7, 15
Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi, Carnevale, ¹³ Dean ¹⁴	§ 103	1–15

In support of their respective positions, Petitioner relies on the Declarations of Mark J. Ratain, M.D. (Exs. 1002, 1200), and Patent Owner relies on the Declaration of Paul E. Oberstein, M.D. (Ex. 2076).

¹¹ Masi, et al., *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*, 15 *Annals of Oncol.* 1766–72 (2004) (Ex. 1012, “Masi”).

¹² Ginocchi, et al., *MODIFIED FOLFOXIRI IN ADVANCED PANCREATIC CANCER*, 23(9 Suppl) *Annals of Oncology* ix238 (2012) (Ex. 1016, “Ginocchi”).

¹³ Carnevale and Ko, *MM-398 (nanoliposomal irinotecan): emergence of a novel therapy for the treatment of advanced pancreatic cancer*, 12 *Future Oncol.* 453–464 (2016) (Ex. 1013, “Carnevale”).

¹⁴ Dean, et al., *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)*, 34(4 Suppl.) *J. Clin. Oncol.* tps482 (2016) (Ex. 1014, “Dean”).

II. ANALYSIS

A. *Principles of Law*

To prevail in this *inter partes* review, Petitioner “shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A claim is unpatentable for obviousness if “the differences between the subject matter sought to be patented and the prior art are 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 to which said subject matter pertains.” 35 U.S.C. § 103 (pre-AIA); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighed en route to the final obviousness determination. *See, e.g., Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of objective indicia, when present, must always be considered in determining obviousness).

We analyze the challenges to patentability in accordance with these principles.

B. *Level of Ordinary Skill in the Art*

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art;

prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

Petitioner asserts that

[t]he person of ordinary skill in the art (POSA) would have been an M.D. and/or Pharm. D who would have completed training in medical oncology, particularly in the field of gastrointestinal (GI) cancers, or a Ph.D. in clinical pharmacology, pharmaceutical sciences, pharmaceuticals, and/or drug delivery, also particularly in the field of GI cancers, or their equivalents, along with at least 1-2 years of post-doctoral experience.

Pet. 26 (citing Ex. 1002 ¶¶ 44–46).

Patent Owner states that, for purposes of this proceeding, it does not dispute Petitioner’s proposed definition of a POSA. PO Resp. 8.

Based on the entirety of the trial record, we adopt Petitioner’s proposed definition of a POSA’s skill level because it is consistent with the skill level reflected in the disclosures of the ’552 patent and prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art may reflect an appropriate level of skill in the art).

We find both parties’ declarants, Drs. Ratain and Oberstein, are qualified to opine from the perspective of a POSA, because each has at least ordinary skill in the art. *See* Ex. 1002 ¶¶ 2–20; Ex. 2076 ¶¶ 5–17.

Petitioner argues that we should give Dr. Oberstein’s opinion little to no weight because Dr. Oberstein benefits financially through providing consulting services on NALIRIFOX to Patent Owner and through prescribing NALIRIFOX. Reply 1–2.

We decline to discount Dr. Oberstein’s opinion based on the alleged conflict of interest and bias. Dr. Oberstein testified that the consulting fees

he receives from Patent Owner reflect a small fraction of his income. Ex. 1210, 402:21–403:9. We also agree with Patent Owner that an oncologist prescribing an FDA-approved regimen does not evince bias. *See* Sur-reply 23; *see also* Ex. 1206, 49 (showing NALIRIFOX is a category 1, NCCN-preferred first-line therapy for metastatic pancreatic cancer), 69 (explaining category 1 is based upon high-level evidence).

Petitioner also contends that Dr. Oberstein “offers conclusory opinions,” “fails to properly apply the law, continues to look at each reference in isolation, refuses to acknowledge logical suggestions in the art, and imports new limitations into the claims.” Reply 3–4. We evaluate each piece of evidence, including Dr. Oberstein’s opinion, as it relates to our substantive patentability analysis, and accord it proper weight.

C. *Claim Construction*

In an *inter partes* review, we construe a claim term “using 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) (2020). Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

1. “treating”/“treat”

Petitioner proposes that the terms “treating” and “treat,” as used in the ’552 claims, should be interpreted as “attempting to cause a therapeutic improvement but not requiring actual efficacy.” Pet. 27 (citing Ex. 1001,

claims 1–15, 2:23–25, 2:27–46, 2:57–65, 18:34–38). As support, Petitioner cites Dr. Ratain’s testimony that:

[t]reating a patient is always with the attempt or intent to cause a therapeutic improvement of the patient, which, in the case of metastatic pancreatic cancer, could be reduced tumor growth or increased overall survival in the patient. However, “treatment” does not require a certain level of efficacy, and oftentimes, treating patients with this disease does not result in therapeutic improvement.

Ex. 1002 ¶ 50.

Petitioner argues that the language of the claims supports its proposed construction because “nothing in the claim language . . . requires that ‘treating’ brings about a particular result, such as clinical efficacy.” Pet. 27 (citing Ex. 1002 ¶ 51). “Instead,” Petitioner continues, “the body of the claims define the method of treatment with structural components – administering specific combination of drugs given at specified doses, frequency . . . and conditions” *Id.*

Petitioner notes that the ’552 patent Summary describes its method of treating pancreatic cancer “solely by administration of the drugs and not by clinical efficacy.” Pet. 28 (citing Ex. 1001, 2:26–46; Ex. 1002 ¶¶ 52–56). In contrast, one of the embodiments describes a method of treating pancreatic cancer, requiring administering to the subject “*a therapeutically effective amount* of MM-398 liposomal irinotecan in combination’ with the other claimed drugs.” *Id.* (citing Ex. 1001, 18:34–38). Petitioner also points to US Provisional application 62/208,209, from which the ’552 patent claims priority, as stating “[a]s used herein, ‘effective treatment’ refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder.” *Id.* (citing Ex. 1015 ¶ 36).

Petitioner argues that

it is clear that the patentees knew how to use the term “therapeutically effective” when describing a particular embodiment of their invention or define “effective treatment” in its provisional application (Ex. 1015, ¶¶ [0036], [0074]-[0076]) ***but deliberately chose to delete*** “therapeutically effective” and “effective treatment” from the claim language, which compels against injecting a therapeutic result into the Challenged Claims.

Pet. 28–29.

In its Preliminary Response, Patent Owner asserted that “the claims cover effective methods of treatment. And [Petitioner]’s proposed construction, which does not require actual efficacy, is at odds with the plain and ordinary meaning of ‘treat’ and ‘treatment.’” Prelim. Resp. 8.

In the DI, the Board stated 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.

DI 14. We, however, rejected the notion that the claims “would require some particular degree of clinical efficacy” because “the level of clinical efficacy is not a claim limitation.” *Id.*

After institution, the parties do not dispute the Board’s construction. *See* PO Resp. 10; Reply 16. Indeed, Patent Owner’s declarant “expressly adopted the Board’s construction of ‘treatment’ and rendered his opinions on non-obviousness under that construction.” Sur-reply 3–4 (citing Ex. 2076 ¶¶ 135–136). Patent Owner, however, points out that Petitioner, in contrast, filed its Reply “***without*** any supporting expert declaration.” *Id.* at 4. As a

result, according to Patent Owner, Petitioner “has *not* offered any expert testimony on obviousness under the Board’s construction of ‘treatment.’” *Id.*

Although Petitioner did not file an expert declaration with its Reply, we disagree with Patent Owner that Petitioner’s declarant did not offer opinion on obviousness under the Board’s construction of “treating”/“treat.” As the Board stated in the DI, Dr. Ratain’s testimony is consistent with the ’552 patent’s disclosure that “patients may or may not receive some therapeutic benefit from the treatment.” DI 13 (citing Ex. 1001, 33:4–9, 40:58–63).

Dr. Ratain testified that

[t]he 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.

Ex. 1002 ¶ 50; *see also* Pet. 27 (citing Ex. 1002 ¶ 50) (same).

With this understanding, Dr. Ratain opined that a POSA would have understood the preamble of claim 1 “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.” Ex. 1002 ¶ 49. Although “the claims do not require that the treatment regimen be superior to any other standard treatment,” Dr. Ratain recognized that “the POSA would expect that the treatment regimen be superior to no treatment in some regard.” *Id.* This testimony is consistent with the Board’s construction, requiring

“treatment” to “have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.”

Patent Owner’s declarant, Dr. Oberstein, offers similar opinions. For example, Dr. Oberstein points to medical dictionaries for defining “treatment” as “the management and care of a patient for the purpose of combating disease or disorder.” Ex. 2076 ¶ 138 (quoting Ex. 2017, 3). According to Dr. Oberstein, “[w]hen administering ‘treatment’ to metastatic pancreatic cancer patients, the goal is always that such treatment will have more than a *de minimis* therapeutic benefit or efficacy for that patient. While some patients may not receive a therapeutic benefit, the intention behind any treatment is for such benefit to occur.” *Id.* ¶ 139; *see also* Ex. 1210, 338:19–339:18 (Dr. Oberstein testifying that, when treating a patient, “the goal of that treatment is to provide benefit to the patient,” but “we don’t know for sure” whether the treatment is going to work).

After reviewing the record developed at trial, we see no reason to change our construction of “treating”/“treat.” In addition, we find Dr. Ratain offered testimony on obviousness with the understanding of “treating”/“treat” consistent with the Board’s construction.

2. “a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas”

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** four recited drugs, each at a specific dosage.

As a follow-up to argument at the hearing, we requested further briefing from the parties on the scope of claim 1 of the '552 patent. Paper 49. We asked the parties to propose construction for the preamble, taking into account the transitional phrases “comprising” and “consisting of” used in the claim. *Id.* at 2.

The parties agree that treating “a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas” refers to first-line therapy. Paper 50, 1; Paper 51, 1. The parties also agree that the transitional phrase “consisting of” “limits the scope of the claimed antineoplastic therapy to **only** the doses specifically listed, and **excludes** any other dose not specified in the claims.” Paper 51, 4–5; *see also* Paper 50, 5 (“[T]he recited antineoplastic therapy must literally ‘consist of’ the four drugs at the specific four recited doses.”). The parties further agree that transitional phrase “comprising” “describes the broader method of treatment, which includes the closed antineoplastic therapy, but can also include other non-antineoplastic therapies . . . including corticosteroids, such as dexamethasone, or anti-emetics, such as a 5-HT3 antagonist.” Paper 51, 5 (citing Ex. 1001, 18:13–17, 24:14–17; claim 15); *see also* Paper 50, 3 n.3 (“The ‘comprising’ transitional language of claim 1 provides that the treatment methods may additionally include other drugs . . . e.g., a corticosteroid and/or anti-emetic.”) (citing Ex. 1001, 24:14–17; claim 15).

The parties agree that “[c]laim 1 does not encompass a method in which the patient is first treated with the recited drugs at the recited doses, and then two weeks later with the same four drugs but with at least one drug in a dose different from that recited.” Paper 50, 5; *see also* Paper 51, 4

(“[W]here ‘in the second administration two weeks later, the patient is treated with the same four drugs, but with at least one drug as a different dose’ from what is recited in claim 1, the claimed method is no longer being practiced.”)

The parties, however, disagree over whether each recited dose must be the starting dose. Petitioner argues that “claim 1 requires that the method of treatment is a first-line therapy, but does not require that the claimed doses be used as a starting dose.” Paper 51, 1. In contrast, Patent Owner argues that “[t]he specification describes that the recited dose of each drug is a ‘starting’ or ‘initial’ dose.” Paper 50, 2 (citing Ex. 1001, 13:38–45, 30:5–7).

For purposes of this Decision, we do not need to resolve this dispute. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating that claim terms need only be construed to the extent necessary to resolve the controversy). As explained below, we agree with Petitioner that, even if claim 1 recites the starting dose for each drug, Petitioner has shown, by a preponderance of the evidence, that the prior art teaches each dose and a POSA would have had a reason to start with the recited doses. *See infra* Section II.G.3; Paper 51, 3 n.2. Because we find that the prior art teaches or suggests the claimed subject matter even under Patent Owner’s proposed narrower claim interpretation, we need not further construe the disputed claim language.

D. Priority Date

The ’552 patent issued from an application filed on November 10, 2017. Ex. 1001, code 22. That application claims priority to several earlier applications, the earliest of which is a provisional application filed on August 21, 2015. *Id.*, code 60.

Petitioner argues that if the claims are construed to require clinical efficacy, then they would not be entitled to priority of the earlier applications “because these applications did not adequately describe methods using the claimed combination of drug doses to show clinical efficacy of metastatic pancreatic cancer in humans.” Pet. 3. Under that scenario, Petitioner contends that the priority date would be November 10, 2017. *Id.*; *see also id.* at 36–39 (same).

Patent Owner asserts that the claims do not require clinical efficacy, and thus, the challenged claims are entitled to the priority date of August 21, 2015. PO Resp. 11, 58.

As explained above, we reject the notion that the claims “would require some particular degree of clinical efficacy” because “the level of clinical efficacy is not a claim limitation.” *See supra* Section II.C.1 (quoting DI 14). As a result, we determine the challenged claims are entitled to the priority date of August 21, 2015.

E. Petitioner’s Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2002, 2003, 2005–2011, 2013–2015, 2020–2035, 2037, 2039–2042, 2047–2072, 2074, and 2075. Paper 43 (“Pet. Mot.”), 1. After Patent Owner filed an Opposition to Petitioner’s Motion (Paper 44, “PO Opp.”), Petitioner filed a Reply in support of its Motion (Paper 48, “Pet. Reply”).

Petitioner, as the moving party, bears the burden of proving that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a); *see also* Trial Practice Guide

(“TPG”)¹⁵ § II.K (“A motion to exclude must explain why the evidence is not admissible.”). For the reasons explained below, we deny Petitioner’s Motion.

1. Exhibit 2004

Petitioner argues that we should exclude Exhibit 2004 because it is irrelevant, confusing, prejudicial, and contains hearsay. Pet. Mot. 2–3 (citing Fed. R. Evid. 401–403, 801, 802). We are not persuaded by Petitioner’s arguments.

Petitioner asserts that “Patent Owner relies on Exhibit 2004 to claim that only 85 mg/m² of oxaliplatin could be used when treating patients with FOLFIRINOX.” Pet. Mot. 2. “Because Patent Owner is relying on statements for the truth of the matter asserted,” Petitioner concludes that “these statements are hearsay.” *Id.*

Patent Owner counters that Exhibit 2004 is not hearsay because “it is offered to establish what a POSA would have understood about FOLFIRINOX from the published literature at the time of the invention.” PO Opp. 2 (citing Ex. 2076 ¶¶ 58, 240). Here, a prior art publication is offered simply as evidence of what it described, not for proving the truth of the matters addressed in the article. Moreover, even if the cited content were considered hearsay, Petitioner has not shown that it would be improper for experts in the field, such as Patent Owner’s experts here, to rely on such disclosure in analyzing alleged obviousness of the challenged claims. *See* Fed. R. Evid. 703. Thus, we decline to exclude Exhibit 2004 as hearsay.

¹⁵ Available at www.uspto.gov/patents/ptab/trial-practice-guide (last updated Dec. 2025).

Petitioner argues that “statements from Exhibit 2004 relied upon by Patent Owner related to FOLFIRINOX dosing are irrelevant, confusing, and unduly prejudicial.” Pet. Mot. 2. According to Petitioner, “Exhibit 2004 does not, contrary to Patent Owner’s suggestion, indicate that any individual understood FOLFIRINOX regimens to be limited to any particular dosing and/or limited to 85 mg/m² of oxaliplatin.” *Id.*

Patent Owner contends that this line of “substantive dispute about what Exhibit 2004 discloses goes to weight, not admissibility, and is not a proper basis for exclusion.” PO Opp. 3. We agree with Patent Owner.

Accordingly, we deny Petitioner’s Motion to Exclude Exhibit 2004.

2. Exhibits 2008 and 2009

Petitioner argues that we should exclude Exhibits 2008 and 2009 because they are irrelevant, confusing, prejudicial, contain hearsay, and are not authenticated. Pet. Mot. 3–4 (citing Fed. R. Evid. 401–403, 801, 802, 901, 902). We are unpersuaded.

Petitioner asserts that Patent Owner and its expert rely on Exhibits 2008 and 2009 “to claim that new clinical trials of oncology drugs face low likelihoods of approval and high fail rates.” Pet. Mot. 3–4 (citing Ex. 2076 ¶ 297). Petitioner argues that “the statements from these exhibits are used for the truth of the matter asserted and thus constitute hearsay.” *Id.* at 4.

Patent Owner counters that Exhibits 2008 and 2009 are not hearsay because they “are offered to establish what was publicly understood about clinical development success rates in oncology—thus are being used to establish what a POSA would have understood regarding the state of the art.” PO Opp. 4. We agree with Patent Owner that Exhibits 2008 and 2009

are offered as evidence of what they describe, not for proving the truth of the matters addressed therein. Therefore, Exhibits 2008 and 2009 do not constitute hearsay.

Petitioner asserts that Exhibits 2008 and 2009 “both relate to the success of clinical trials, not the obviousness of a drug combination, which are two very different standards.” Pet. Mot. 4. According to Petitioner, “use of such evidence is likely to cause confusion and create undue prejudice.” We are not persuaded.

Similar to a district court in a bench trial, the Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. Thus, in this *inter partes* review, the better course is to have a complete record of the evidence to facilitate public access as well as appellate review.

Petitioner further raises technical arguments about the substantive content in Exhibits 2008 and 2009. Pet. Mot. 4 (arguing that certain data were not considered in the analyses and that delivery technology could affect success rate). Such discussion goes to weight, not admissibility, and is not a proper basis for exclusion.

Lastly, Petitioner contends that “Patent Owner has not provided any evidence that either exhibit is an authentic document published and available prior to the priority date.” Pet. Mot. 4. Patent Owner filed a declaration from a librarian, who sufficiently addressed the authenticity and background of Exhibits 2008 and 2009. Ex. 2077 ¶¶ 13–19.

Accordingly, we deny Petitioner’s Motion to Exclude Exhibits 2008 and 2009.

3. Exhibit 2010

Petitioner argues that we should exclude Exhibit 2010 because it is irrelevant, confusing, prejudicial, and contains hearsay. Pet. Mot. 5 (citing Fed. R. Evid. 401–403, 801, 802). We are not persuaded by Petitioner’s arguments.

Petitioner asserts that “Patent Owner and its expert rely on Exhibit 2010 to claim that phase II clinical trials of oncology drugs have a low predictive value of FDA approval.” Pet. Mot. 5. Petitioner argues that the statements relied upon are hearsay because they are used for the truth of the matter asserted. *Id.*

Patent Owner counters that Exhibit 2010 is not hearsay because it is offered to “provide an understanding as to what a POSA would have understood from the art at the time of the invention.” PO Opp. 7. We agree with Patent Owner that because Exhibit 2010 is offered as evidence of what it describes, not for proving the truth of the matters addressed therein. Therefore, Exhibit 2010 does not constitute hearsay.

Petitioner contends that Exhibit 2010 “compares clinical trial success and FDA approval, neither of which relate to whether a proposed drug combination is obvious.” Pet. Mot. 5. According to Petitioner, “use of such evidence is likely to cause confusion and create undue prejudice.” *Id.*

As explained above when discussing Exhibits 2008 and 2009, the Board acts as both the gatekeeper of evidence and as the weigher of evidence. Rather than excluding evidence that is allegedly irrelevant or confusing, we will simply not rely on it or give it little weight, as appropriate, in our analysis.

Accordingly, we deny Petitioner’s Motion to Exclude Exhibit 2010.

4. Other Exhibits

Petitioner seeks to exclude Exhibits 2002, 2003, 2005–2011, 2013–2015, 2020–2028, 2030, 2033–2035, 2037, 2039–2042, 2047–2072, 2074, and 2075 because they “are not discussed or cited anywhere in Patent Owner’s Response (Paper 21) or Patent Owner’s Sur-Reply (Paper 38).” Pet. Mot. 6.

Patent Owner counters that “many of the challenged exhibits are in fact cited directly and are substantively discussed in Dr. Oberstein’s declaration.” PO Opp. 9. According to Patent Owner, its Response and Sur-Reply “cite to Dr. Oberstein’s discussion and/or reliance on those exhibits.” *Id.* Patent Owner provides a table, pointing to the record where the challenged exhibits were cited. *Id.* at 9–10. Patent Owner asserts that the remaining exhibits were cited and relied upon by Patent Owner in its Preliminary Response (Paper 9) and/or its request for discretionary denial (Paper 8). *Id.* at 11–12. Patent Owner argues that pre-institution papers are part of the record of this proceeding. *Id.* at 11.

Rather than exclude these exhibits, the Board generally does not rely on exhibits that have not been properly cited and/or explained by the parties in their substantive trial briefing. We are unpersuaded that the challenged exhibits should be excluded here.

Accordingly, we deny Petitioner’s Motion to Exclude Exhibits 2002, 2003, 2005–2011, 2013–2015, 2020–2028, 2030, 2033–2035, 2037, 2039–2042, 2047–2072, 2074, and 2075.

F. Patent Owner’s Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1004 and 1017, as well as portions of the Ratain declaration (Ex. 1002) and deposition

(Ex. 2073) that rely on Exhibits 1004 and 1017. Paper 42 (“PO Mot.”), 1, 13. Petitioner filed an Opposition to Patent Owner’s Motion (Paper 45, “Pet. Opp.”), and Patent Owner filed a Reply in support of its Motion (Paper 47, “PO Reply”).

Patent Owner, as the moving party, bears the burden of proving that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a). For the reasons explained below, we deny Patent Owner’s Motion.

1. Violation of 37 C.F.R. § 42.63(b)

Patent Owner argues that Exhibit 1004 violates 37 C.F.R. § 42.63(b). PO Mot. 1, 3, 7. Exhibit 1004 is described as “Certified English Translation of the Protocol of Conroy.” Pet. 5. Patent Owner points out that Petitioner did not file “an affidavit attesting to the accuracy of the translation,” as required by 37 C.F.R. § 42.63(b), at the time of filing Exhibit 1004 and the Petition. PO Mot. 1, 3, 7. Patent Owner contends that because Petitioner did not respond to Patent Owner’s objection of Exhibit 1004 by timely serving supplemental evidence, “[t]he window for cure has closed.” *Id.* at 7. We are not persuaded by Patent Owner’s argument.

As explained below, we find the filing of Exhibit 1204 as well as the service and filing of Exhibit 1004A have sufficiently satisfied the requirement for certification of the translation of Exhibit 1004, as required by 37 C.F.R. § 42.63(b). *See infra* Section II.G.1. Accordingly, we deny Patent Owner’s Motion to exclude Exhibit 1004 for allegedly violating 37 C.F.R. § 42.63(b).

2. Authentication

Patent Owner asserts that we should exclude Exhibits 1004 and 1017 because neither is authenticated. PO Mot. 8–11 (citing Fed. R. Evid. 901(a)). Petitioner counters that both Exhibits 1004 and 1017 have been authenticated and/or are self-authenticating. Pet. Opp. 4–6, 8–10. According to Petitioner, both exhibits contain “multiple, robust indicia of authenticity that satisfy FRE 901(a).” *Id.* at 4. We find Petitioner’s argument persuasive.

As Petitioner points out, Conroy (Ex. 1003) was published in the well “respected and reputable New England Journal of Medicine (‘NEJM’) in 2011.” Pet. Opp. 2. Patent Owner does not challenge the authenticity of the NEJM publication or Conroy article itself. *Id.* Thus, we agree with Petitioner that the fact that both Conroy Protocol (Ex. 1004) and Conroy Appendix (Ex. 1017) are referenced in Exhibit 1003 underscores the authenticity of these documents. *Id.*

Indeed, Conroy provides a hyperlink to Conroy Protocol, stating that “[t]he protocol, including the statistical analysis plan, is available with the full text of this article at NEMJ.org. The first author vouches for the fidelity of the study to the protocol.” Ex. 1003, 3.¹⁶ We acknowledge that the protocol through the hyperlink provided by NEMJ is in French. Patent Owner, however, does not challenge the accuracy of the translation in Exhibit 1004. Furthermore, as explained below, we find the filing of Exhibit 1204 and the service and filing of Exhibit 1004A sufficiently satisfy the certified translation requirement under 37 C.F.R. § 42.63(b) as to Exhibit 1004. *See infra* Section II.G.1. As a result, we are persuaded that

¹⁶ Unless otherwise noted, we cite the page numbers of the exhibits, not the native page numbers.

Exhibit 1004 is an admissible translation of a self-authenticating document. *See* FRE 902(6) (prescribing that printed material purporting to be a periodical is self-authenticating).

Similarly, Conroy refers to Exhibit 1017, stating that it is “available at NEMJ.org.” Ex. 1003, 1, 3. As Patent Owner acknowledges, NEMJ made Exhibit 1017 accessible through a hyperlink from the Conroy article page. PO Mot. 10. As a result, we agree with Petitioner that “[t]he fact that the Conroy Appendix [Ex. 1017] was published by a publication like NEJM makes it self-authenticating under at least FRE 902(6).” Pet. Opp. 8.

We are further persuaded by Petitioner’s arguments that both Exhibits 1004 and 1017 offer other indicia of authenticity. Pet. Opp. 6 (arguing that Exhibit 1004 is a clinical trial protocol bearing “hallmarks of a genuine study protocol document”), 10 (arguing that the information in Exhibit 1017 “corroborates its authenticity and its identification as the operative Conroy Appendix”). Thus, we find Petitioner has provided sufficient evidence to authenticate Exhibits 1004 and 1017. *See* Fed. R. Evid. 901(b)(4) (prescribing that “[t]he appearance, contents, substance, internal patterns, or other distinctive characteristics of the item, taken together with all the circumstances” satisfies the authentication requirement).

Accordingly, we deny Patent Owner’s Motion to Exclude Exhibits 1004 and 1017 for alleged lack of authentication.

3. Hearsay

Patent Owner also argues that to the extent Petitioner relies on any dates appearing in Exhibits 1004 and 1017 to establish the public

accessibility of those exhibits, those dates are hearsay. PO Mot. 9, 11–12 (citing Fed. R. Evid. 801(c)). We are not persuaded by this argument.

As we understand it, Petitioner does not rely on the dates appearing in Exhibits 1004 and 1017 to establish the public accessibility of those exhibits. Instead, Petitioner relies on statement in Conroy (Exhibit 1003) for that purpose. *See* Pet. 16 (citing Exhibit 1003 for stating that Conroy Protocol was “available with the full text of this article at NEMJ.org”); Pet. Opp. 8–9 (citing Exhibit 1003 for stating that Conroy Appendix was “available at NEMJ.org”). Patent Owner did not object to, and does not seek to exclude, Exhibit 1003. Accordingly, we deny Patent Owner’s Motion to Exclude Exhibits 1004 and 1017 for alleged hearsay.

4. Exhibits 1002 and 2073

Because we do not exclude Exhibits 1004 and 1017, we also do not exclude portions of the Ratain declaration (Ex. 1002) and deposition (Ex. 2073) that rely on Exhibits 1004 and 1017.

G. *Alleged Obviousness of Claims 1, 3–6, and 8–14*

Petitioner asserts that claims 1, 3–6, and 8–14 would have been obvious over the combination of Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, and Cantore. Pet. 39–58. After reviewing the entire record developed at trial, and as explained below, we determine Petitioner has shown by a preponderance of the evidence that the asserted combination of prior art renders the challenged claims obvious.

1. Prior Art Status of Conroy Protocol and Conroy Appendix

Patent Owner argues that Petitioner did not provide, as required under 37 C.F.R. § 42.63(b), a certification of translation of Conroy Protocol (Ex. 1004) along with its Petition. PO Resp. 13. Patent Owner also argues

that Petitioner has not shown that either Conroy Protocol or Conroy Appendix “is a printed publication, including the date by which [they] became publicly available.” *Id.* We address these arguments in turn.

a. Certification of Translation

Petitioner filed the translation certification for Conroy Protocol with its response to Patent Owner’s request for discretionary denial. *See* Ex. 1204. Exhibit 1204 includes three certifications, accounting for the entire translation of Conroy Protocol. *Id.* All three certifications were dated prior to the filing of the Petition and filed before the institution of trial. *Id.*

In addition, the record shows that, after institution, Petitioner timely responded to Patent Owner’s objection of Exhibit 1004, including serving Exhibit 1004A. Ex. 1004A, 89, 90; Ex. 1223 ¶¶ 2, 3; Ex. 1224, 2–3. According to Petitioner, Exhibit 1004A includes certification of Exhibit 1004. Ex. 1224, 3.

Patent Owner points out that Exhibit 1004A does not include certification of the translation of pages 38 to 60 of Conroy Protocol, which is “a substantial portion of the exhibit.” PO Reply 1. That is a rather unfortunate fact. We note, however, the two certifications included in Exhibit 1004A are the same as two of the three certifications included in Exhibit 1204. *Compare* Ex. 1004A, 89, 90, *with* Ex. 1204, 1, 3. Thus, Petitioner’s failure to include the third certification Exhibit 1004A appears to be an oversight. We do not trivialize the consequence of human error in a legal proceeding. We, however, deem this mistake harmless because Petitioner had filed Exhibit 1204 before trial institution. In other words, both the Board and Patent Owner had possession of all the translation certifications, before Patent Owner even objected to Exhibit 1004.

In sum, Patent Owner has not identified any prejudice based on the delayed filing of the translation certifications. Under these circumstances, we find that Petitioner has sufficiently satisfied the requirement for certification of the translation of Exhibit 1004, as required by 37 C.F.R. § 42.63(b).¹⁷

b. Printed Publication

A petitioner in an *inter partes* review may challenge claims of a patent “only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.” 35 U.S.C. § 311(b). Whether a reference qualifies as a “printed publication” involves a case-by-case inquiry into the facts and circumstances surrounding the reference’s disclosure to the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). A reference is publicly accessible upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence can locate it. *Kyocera Wireless Corp. v. ITC*, 545 F.3d 1340, 1350–51 (Fed. Cir. 2008).

Conroy was published on May 12, 2011. Ex. 1003, 1. Conroy refers to Conroy Protocol (Ex. 1004), stating that “[t]he protocol, including the statistical analysis plan, is available with the full text of this article at NEMJ.org.” Ex. 1003, 3. When questioned whether he has “any reason to believe that the protocol would not have been provided on NEJM.org with this text when it was published,” Dr. Oberstein testified that “if they say they provided it, then I think they probably provided it.” Ex. 1210, 165:20–166:2.

¹⁷ Alternatively, to the extent necessary, under the circumstances of this case, we waive the requirement of § 42.63(b). *See* 37.C.F.R. § 42.5(b).

In addition, Dr. Ratain testified that “most top journals require that the protocol be submitted at the time of initial submission, and it’s always published alongside any major paper.” Ex. 2073, 42:2–5. According to Dr. Ratain, “[c]ertainly, New England Journal of Medicine does that.” *Id.* at 42:6–7.

We credit the testimony from both Dr. Oberstein and Dr. Ratain on this issue. Accordingly, we find Exhibit 1004 was publicly accessible at the same time Conroy was published.

Similarly, Conroy refers to Conroy Appendix (Ex. 1017), stating that it is “available at NEMJ.org.” Ex. 1003, 1, 3. Dr. Oberstein testified that such a statement means NEJM provided Conroy Appendix. Ex. 1210, 166:3–16. We credit the testimony from Dr. Oberstein on this issue. Accordingly, we find Exhibit 1017 was publicly accessible at the same time Conroy was published.

2. Relevant Prior Art Disclosure

a. Conroy

Conroy reports a phase 2–3 clinical trial “of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer.” Ex. 1003, 1. Conroy teaches that “[t]he median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months).” *Id.* at 6. Thus, Conroy concludes that “FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status.” *Id.*

Conroy refers to Conroy Protocol for details of the treatment plan. *Id.* at 3. Conroy summarizes 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. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg per square meter over a 46-hour period every 2 weeks.

Id. at 3.

Conroy teaches that “[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.” *Id.* at 4. In addition, Conroy teaches that “[i]n the event of predefined toxic events, protocol-specified treatment modifications were permitted.” *Id.* at 3. Conroy refers to Conroy Appendix for details of the modifications. *Id.*

b. Conroy Protocol

Conroy Protocol provides supplemental material for the Conroy paper. Ex. 1004, 1; *see also* Ex. 1003, 3 (“The protocol, including the statistical analysis plan, is available with the full text of this article at NEMJ.org. The first author vouches for the fidelity of the study to the protocol.”). It teaches FOLFIRINOX treatment regimen as well as dose reductions due to toxicities. Ex. 1004, 14, 16–18.

The dose reduction plan due to hematological toxicity based on biological results at day fifteen is reproduced below:

TREATMENT A: Folfirinnox

CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU
PNN $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$	No cycle delay	No dose reduction		
PNN $< 1.5 \times 10^9/L$	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, discontinuation of treatment*	<u>1st episode</u> : dose reduction to 150 mg/m ² <u>2nd episode</u> : dose maintained at 150 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : no dose reduction <u>2nd episode</u> : reduce dose to 60 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : eliminate bolus on D1
Platelets $< 75 \times 10^9/L$	Delay treatment until recovery (platelets $\geq 75 \times 10^9/L$) If no recovery at D29, discontinuation of treatment	<u>1st episode</u> : no dose reduction <u>2nd episode</u> : reduce dose to 150 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : reduce dose to 60 mg/m ² <u>2nd episode</u> : maintenance of reduced dose <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : reduce bolus and continuous infusion dose by 25%

* If there is no recovery after 2 treatment delays, discontinue treatment unless there is a clear clinical benefit: the case will then be discussed with the study coordinator and the sponsor.

Ex. 1004, 16. The table reproduced above instructs that, for patients with certain toxicity events, reduce irinotecan dose to 150 mg/m², reduce oxaliplatin dose to 60 mg/m², and eliminate bolus 5-FU. *Id.*

c. Conroy Appendix

Conroy Appendix also provides supplemental material for the Conroy paper. Ex. 1017, 1; *see also* Ex. 1003, 3 (“In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see the Supplementary Appendix, available at NEJM.org).”). Conroy Appendix discusses dose reductions, teaching reducing irinotecan dose to 150 mg/m², oxaliplatin dose to 60 mg/m², and eliminating 5-FU. Ex. 1017, 3–7.

d. Mahaseth

Mahaseth reports “a modified FOLFIRINOX regimen in both locally advanced unresectable and metastatic PC [pancreatic cancer] patients with good performance status.” Ex. 1005, 1. Mahaseth teaches that its

modified FOLFIRINOX regimen included oxaliplatin 85 mg/m² in water with 5% dextrose intravenously (IV) over 2 hours, leucovorin 400 mg/m² in normal saline IV over 90 minutes concurrently with irinotecan 180 mg/m² in normal saline IV over 90 minutes, and 5-FU 2400 mg/m² in water with 5% dextrose via continuous intravenous infusion over 46 hours. Patients did not receive bolus 5-FU.

Id. at 2.

In Mahaseth, “[e]ighteen patients required dose reduction. Four patients had only oxaliplatin held due to neuropathy. Five patients had only irinotecan held or reduced due to diarrhea. Nine patients had dose reduction of all agents.” Ex. 1005, 3.

Mahaseth teaches the “modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC.” *Id.* at 5. “The modified FOLFIRINOX regimen appears to have an improved safety profile especially with respect to neutropenia, fatigue, and vomiting.” *Id.* at 4. In addition, median progression-free survival (PFS) and overall survival (OS) in patients with stage II/III pancreatic cancer treated with the modified FOLFIRINOX regimen are 13.7 and 17.8 months, respectively. *Id.* For reference, Conroy reported that the median PFS and OS in patients treated with FOLFIRINOX were 6.4 and 11.1 months, respectively. *Id.* at 1.

e. Bayever

Bayever teaches “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.” Ex. 1006, 4.

Specifically, Bayever teaches a study design for treating patients with MM-398 80 mg/m² IV over 90 minutes, every 2 weeks. Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m². If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m².

5-FU 2400 mg/m² IV over 46-hours, every 2 weeks.

Levoleucovorin dosed at 200 mg/m² or the l + d racemic mixture dosed at 400 mg/m², IV over 30 minutes, every 2 weeks.

Id. at 26–27.

Bayever states that the “stable liposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index.” *Id.* at 10.

f. Saif

Saif reports the results of a randomized large phase III study called the NAPOLI-1 study. Ex. 1007, 1. “This study treated patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy.” *Id.*

NAPOLI-1 results showed that “the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin 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.”

Ex. 1007, 1.

Saif asks: “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?”

Ex. 1007, 1. Saif states that “[i]t 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.*

g. Ko

Ko teaches that liposomal irinotecan PEP02, also known as MM-398, has been shown in preclinical studies to improve pharmacokinetics and tumour bio-distribution of both irinotecan and its active metabolite SN-38 when compared with the free form of the drug, with less accumulation in many of the target organs associated with toxic side effects. PEP02 also demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model.

Ex. 1008, 2; *see also id.* at 1 (teaching that MM-398 “has improved pharmacokinetics and tumour bio-distribution of the free drug”).

Ko reports that in a phase 2 study, monotherapy liposomal irinotecan PEP02/MM-398 “demonstrates moderate antitumour activity with a manageable side effect profile for metastatic, gemcitabine-refractory pancreatic cancer patients.” Ex. 1008, 1; *see also id.* at 2 (“PEP02 did show clear evidence of antitumour activity in a subset of patients in whom no standard of care therapy otherwise exists.”).

Ko states that

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

Ex. 1008, 5.

h. Cantore

Cantore teaches that “[i]n vitro studies have shown cytotoxic synergism between oxaliplatin and the active metabolite of irinotecan, and this combination has also shown signs of antitumour activity in patients with pancreatic cancer.” Ex. 1009, 2; *see also id.* at 4 (teaching that irinotecan and oxaliplatin “have shown cytotoxic synergism in vitro and in vivo, with no overlapping toxicity”). Cantore reports a phase II study designed “to determine whether combined therapy with oxaliplatin and irinotecan could have utility as a second- or third-line approach to the treatment of pancreatic cancer that had progressed after first-line treatment with a gemcitabine-containing regimen.” *Id.* at 2.

Cantore teaches treating patients with “oxaliplatin 60 mg/m², administered as a 2-hour intravenous infusion on days 1 + 15, followed by irinotecan 60 mg/m², given as a 30-min intravenous infusion on days 1 + 8 + 15. Treatment cycles were repeated every 4 weeks.” Ex. 1009, 2. According to Cantore, “[d]rug doses could be reduced by 25% if grade 3–4 haematological toxicity or any grade 3 non-haematological toxicity occurred.” *Id.*

Cantore concludes that

combination of irinotecan plus oxaliplatin is a well-tolerated second- or third-line systemic treatment that shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer who have a high performance status and progressive disease despite having previously been treated with a gemcitabine-containing regimen.

Ex. 1009, 5.

3. Claim 1

Petitioner argues that the asserted prior art combination teaches or suggests each limitation of claim 1. Pet. 40–41 (claim chart mapping claim 1’s limitations to prior art teachings).

Specifically, Petitioner asserts that “Conroy, the Conroy Protocol, the Conroy Appendix, and Mahaseth disclosed every feature of this claim, including the claimed 60 mg/m² oxaliplatin, except that they used free irinotecan instead of liposomal irinotecan.” Pet. 41 (“Cantore, the Conroy Protocol, and the Conroy Appendix disclose that 60 mg/m² oxaliplatin was safe and effective in treating metastatic pancreatic cancer when administered with irinotecan every two weeks.”) (emphases removed); *see also id.* at 46 (“[L]owering 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.”).

Petitioner asserts that “the POSA would have been motivated to replace free-irinotecan with liposomal irinotecan in view of Bayever, which by then had already disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims along with the exact same claimed doses of leucovorin and 5-FU.” Pet. 42. According to Petitioner, this is further supported by Saif and Ko, both of which “suggested evaluating MM-398 liposomal irinotecan in first-line therapy.” *Id.*

Petitioner summarizes that

the prior art provided a clear roadmap for a person of ordinary skill in the art (POSA) to make routine, predictable modifications to the FOLFIRINOX regimen to manage its known toxicity. The prior art explicitly suggested substituting liposomal irinotecan for free irinotecan at 60 mg/m² (Saif, Ko,

Bayever), reducing the oxaliplatin dose to 60 mg/m² (Conroy Protocol/Appendix), and omitting the 5-FU bolus (Conroy Protocol/Appendix, Mahaseth, Bayever).

Reply 1.

Petitioner further contends that because “the prior art showed each component of the claimed invention had known efficacy in treating pancreatic cancer,” and “because the claimed doses were in known ranges of use and the doses had all been used or proposed, a POSA had a reasonable expectation of success in arriving at the claimed invention.” Reply 15–16.

Patent Owner disagrees. According to Patent Owner, Petitioner’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.

PO Resp. 23.

Patent Owner contends that the prior art does not teach or suggest the starting dose of 60 mg/m² for oxaliplatin. PO Resp. 26–32. Patent Owner argues that the prior art does not motivate the substitution of liposomal irinotecan for the free drug, let alone in a FOLFIRINOX regimen that also includes 60 mg/m² oxaliplatin and omits bolus 5-FU. *Id.* at 35–40. Patent Owner asserts that the prior art does not motivate the claimed dose of liposomal irinotecan. *Id.* at 40–41.

Patent Owner argues that Petitioner fails to “articulate motivation to make all four of the required modifications at once.” PO Resp. 24; *see also*

id. at 32–35 (“General Toxicity Concerns Would Not Have Motivated the Multiple, Specific FOLFIRINOX Modifications Necessary to Arrive at the Invention”). Patent Owner further argues that Petitioner fails to show reasonable expectation of success. PO Resp. 42–50. In addition, Patent Owner alleges that unexpected results support non-obviousness. *Id.* at 50–53.

On this record, we find Petitioner’s argument persuasive. We explain our reasoning below.

a. 60 mg/m² Oxaliplatin

Prior art teaches FOLFIRINOX as a first-line therapy for metastatic pancreatic cancer. Ex. 1003, 1; Ex. 1004, 4; Ex. 1005, 1. The antineoplastic therapy was administered once every two weeks. Ex. 1003, 1, 3 (patients received FOLFIRINOX “every 2 weeks”); Ex. 1004, 5 (“Cycle restart at D15.”); Ex. 1005, 2 (“Each cycle of therapy consisted of days 1 and 15 treatments.”).

We acknowledge Patent Owner’s argument that the Conroy references and subsequent references all “define FOLFIRINOX as a regimen that comprises 85 mg/m² oxaliplatin.” PO Resp. 27–28 (citing Ex. 1003, 1, 3; Ex. 1004, 15; Ex. 1041, 2–3; Ex. 2004, 1–2). Indeed, it is undisputed that the starting dose for oxaliplatin in Conroy was 85 mg/m². Ex. 1003, 1, 3. Conroy, however, also teaches that “doses were reduced” in FOLFIRINOX administration in the event of predefined toxic events, such as grade 2, 3, or 4 neutropenia. *Id.* at 3. In fact, both Conroy Protocol and Conroy Appendix teach oxaliplatin dose reduction to 60 mg/m² if necessary. Ex. 1004, 16–18; Ex. 1017, 3–7.

Petitioner argues that

these oxaliplatin dose reductions along with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m² dose would indicate to a POSA that a significant portion of the patients undergoing the FOLFIRINOX trial were administered with 60 mg/m² based on various toxicity events.

Pet. 16 (citing Ex. 1002 ¶ 105; Ex. 1003, 4); *see also id.* at 41–42 (citing Ex. 1002 ¶¶ 105, 241–243) (same).

Patent Owner argues that “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,” “or how many dose reductions of oxaliplatin occurred along with other modifications.” PO Resp. 30 (citing Ex. 2073, 84:9–12; Ex. 2076 ¶¶ 151–153, 241, 242). Dr. Oberstein, however, testified that, over the course of the Conroy study, because “a significant number of patients experience[ed]” neutropenia, half of the patients received oxaliplatin with dose of less than 78% of the standard 85 mg/m² dose. Ex. 1210, 163:14–164:6, 252:23–253:11; *see also* Ex. 1003, 8, Table 3 (showing that 45.7% of patients treated with FOLFIRINOX suffered grade 3 or 4 neutropenia).

Patent Owner asserts that Conroy’s dose-adjustment protocol would not have motivated reducing the oxaliplatin dose to 60 mg/m². PO Resp. 29–32. According to Patent Owner, “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.” *Id.* at 29–30. Patent Owner emphasizes the significance

of 85 mg/m² as the starting oxaliplatin dose, arguing that it “is supported by data and rationale.” *Id.* at 28–29 (citing Ychou,¹⁸ 1, 7–8).

Ychou, which Patent Owner cites for support, aimed “to determine the maximum-tolerated dose (MTD) and the recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors.” *Id.* It is worth noting that among the forty-one patients treated, only six had pancreatic cancer, the subject condition of the challenged claims. Ex. 2038, 4 (Table 1).

Ychou treated patients with oxaliplatin/irinotecan at doses of 60/90, 60/120, 85/120, 85/150, 85/180, 85/200, and 85/220 mg/m². *Id.* at 1. Even though Ychou ultimately recommended 85/180 mg/m² of oxaliplatin and irinotecan, it reported that “[r]esponses were observed at nearly all dose levels.” *Id.* at 6.

Ychou observed “11 objective responses,” including three complete responses and eight partial responses, among “34 patients evaluable for efficacy.” Ex. 2038, 5. Notably, among the three complete responses, two were from treatment with 60 mg/m² of oxaliplatin, with the lowest doses of irinotecan (i.e., 60/90 and 60/120 mg/m² of oxaliplatin/irinotecan). *Id.* at 7 (Table 5). The third complete response came from treatment with the maximum-tolerated dose of 85/220 mg/m², at which point half of the evaluable patients experienced severe neutropenia. *Id.* at 3–4, 7. Treatment

¹⁸ Ychou, et al., *An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-Fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors*, 14 Ann. Oncol. 481–89 (2003) (Ex. 2038, “Ychou”).

with 60/120 mg/m² oxaliplatin/irinotecan also generated one of the eight partial responses. *Id.* at 7 (Table 5).

Thus, despite recommending 85 mg/m² of oxaliplatin, Ychou presented data showing efficacy with 60 mg/m² of oxaliplatin as the starting dose. Ex. 2038, 7 (Table 5).

In addition, Ychou was published in 2003, reporting a phase 1 trial, eight years before Conroy's reporting of its phase 2–3 trial in 2011. Ex. 2038, 1. Because Ychou “assessed for the first time” the combination of LV5FU2 with “new drugs, irinotecan and oxaliplatin” (*id.* at 2), it had limited data to evaluate the severity and pervasiveness of the treatment's toxicity.

By the time of Conroy, it was known 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.” Ex. 1003, 8; *see also* Ex. 1041, 3 (same); Ex. 1042, 1 (same). As Dr. Oberstein explained, “[f]ollowing FOLFIRINOX's establishment as a preferred first-line treatment approach, clinicians began employing modified dosing strategies for its individual components to mitigate the toxicity concerns associated with this combination chemotherapy protocol.” Ex. 2076 ¶ 58. The modifications include reduction of oxaliplatin starting dose. *See, e.g., id.* Appendix B, 3 (showing that “Lowrey 2012” administered “Median Starting Dose 80% of that used in PRODIGE/ACCORD trial”¹⁹ in a first-line therapy, and that in

¹⁹ The PRODIGE/ACCORD trial is the trial reported in Conroy. *See* Ex. 1041, 2 (discuss reference 17 under “PRODIGE 4/ACCORD 11 Study in Metastatic Pancreatic Cancer”), 7 (showing reference 17 is Conroy).

“Alessandretti 2013,” “Median Reductions in Dose Compared to FOLFIRINOX” includes “Oxaliplatin: 23.3%” in the first cycle); *see also* Ex. 1216 (“The starting dose intensity of FOLFIRINOX induction therapy was 80 % of that used in the PRODIGE/ACCORD trial. Dose reductions or delays were instituted at the discretion of the treating medical oncologist.”).

Patent Owner nevertheless argues that a POSA “would not readily depart” from oxaliplatin starting dose of 85 mg/m² because “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.” PO Resp. 29 (citing Ex. 2076 ¶¶ 50, 245); *see also id.* at 34 (same). To support this argument, Patent Owner relies on Dr. Oberstein’s testimony that

[w]hen treatment is being given with the goal of long term benefit, “it is important to try to maintain dose intensity, because in both [curative and adjuvant] situations there is a steep dose-response curve, and a small decrease in dose intensity can lead to significant decrease in response and cure rates.” [Ex. 1050, 2.] In light of this, especially in the context of first-line chemotherapy, where the benefit is potentially greatest, it is important to administer the maximum tolerable dose of the therapeutic agents to the patient.

Ex. 2076 ¶ 50. Patent Owner’s argument and Dr. Oberstein’s testimony does not undermine Petitioner’s challenge.

Indeed, Dr. Oberstein neglected that, in the same paragraph he quotes from, Exhibit 1050 teaches that

[f]or the palliative situation of incurable metastatic disease, the situation is different; whilst the effect of dose intensity on response rates has been demonstrated, it should be remembered that the aim is palliation, and that the survival advantage is often small. In this group, more efforts should be made to avoid toxicity, which can be aided by pharmacological considerations.

Ex. 1050, 2.

As Patent Owner acknowledges, metastatic pancreatic cancer carries a poor prognosis, with the median overall survival being less than one year, and the five-year survival rate being approximately 2%. PO Resp. 4 (citing Ex. 2076 ¶¶ 47–50). Thus, we agree with Petitioner that metastatic pancreatic cancer fits more under the “palliative situation” (*see* Reply 7 (citing Ex. 1002 ¶¶ 79, 80; Ex. 1050, 2)), rather than the “curative and adjuvant” situations, to which Dr. Oberstein testified (Ex. 2076 ¶ 50). *See* Ex. 1051, 2 (“Patients with metastatic or recurrent disease were designated as receiving chemotherapy with palliative intent.”).

Our understanding is further supported by other prior art on this record. For example, after observing the toxicities in Conroy, prior art cautioned that “[t]he incidence of severe toxicities is of paramount concern when weighing the risks and benefits of various therapies to determine which to offer patients in a *noncurative setting*.” Ex. 1042, 1 (emphasis added).

Dr. Ratain opined that “[p]reemptive dose reductions are . . . common when the treatment intent is palliative rather than curative.” Ex. 1002 ¶ 80. We credit Dr. Ratain’s testimony because it is consistent with the prior art teaching. *See, e.g.*, Ex. 1050, 2 (Table 2) (suggesting “[d]efinitely consider dose modifications” because “significant toxicity is generally not acceptable” in palliative setting). Thus, we find persuasive Petitioner’s argument that a POSA, aware of FOLFIRINOX’s toxicities, would have considered and had reasons for preemptively reducing the dose of oxaliplatin. *See* Pet. 41–42 (citing Ex. 1002 ¶¶ 105, 241–243), 43–44 (citing Ex. 1002 ¶¶ 97, 105, 106, 241, 242).

Patent Owner asserts that “[a]part from the Conroy references, [Petitioner] CSPC identifies no other basis for alleged motivation to modify FOLFIRINOX by preemptively reducing the dose of oxaliplatin to 60 mg/m².” PO Resp. 31. We disagree with this assertion.

In its claim chart, Petitioner argued that “**Cantore**, the **Conroy Protocol**, and the **Conroy Appendix** disclose that 60 mg/m² oxaliplatin was safe and effective in treating metastatic pancreatic cancer when administered with irinotecan every two weeks.” Pet. 41; *see also id.* at 46 (“Cantore discloses that 60 mg/m² oxaliplatin with irinotecan ‘shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer,’ and no patients were ever reported in Cantore to have to resort to higher doses of oxaliplatin.”) (quoting Ex. 1009, 5).

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.” Ex. 2073, 39:24–41:16). Relying on this testimony, Patent Owner asserts that Petitioner’s reliance on Cantore is based on impermissible hindsight. PO Resp. 26. We disagree.

“Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning.” *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). “[B]ut so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant’s disclosure, such a reconstruction is proper.” *Id.*

Here, it is undisputed that Cantore’s teaching of 60 mg/m² oxaliplatin was knowledge available at the time of the ’552 patent. In fact, Patent Owner emphasizes that “Cantore appears to predate Conroy and the

emergence of FOLFIRINOX as the first-line standard by over six years.” PO Resp. 19. Thus, Patent Owner continues, “Cantore does not reflect all information that would have been available to a POSA as of the effective filing date.” *Id.* We agree with Patent Owner’s observation and argument on this issue. Petitioner, however, does not solely rely on Cantore for teaching 60 mg/m² oxaliplatin. Instead, Petitioner also relies on the Conroy references, which also teach oxaliplatin at the dosage of 60 mg/m². *See* Pet. 41.

As Petitioner points out, “Conroy Protocol/Appendix provided dose-reduction rules and the only reduced dose for the administration of oxaliplatin identified was 60 mg/m².” Reply 11 (Citing Ex. 1004, 16; Ex. 1017, 4–7). In view of the teachings of Cantore and the Conroy references, we agree with Petitioner that “[a] POSA looking to preemptively avoid some of the noted toxicity concerns” would have considered administering a starting oxaliplatin dose at 60 mg/m². *Id.* at 12.

b. 60 mg/m² Liposomal Irinotecan, Leucovorin, and 5-FU

Petitioner relies on the Conroy references as well as Bayever, Saif, and Ko for teaching the doses of liposomal irinotecan, leucovorin, and 5-FU. Pet. 40–41 (claim chart mapping these limitations to the prior art teachings).

Patent Owner counters that “a POSA would not have understood any allegedly superior properties of liposomal irinotecan to translate to a superior combination therapy.” PO Resp. 36. Patent Owner also argues that the prior art as a whole does not motivate the claimed dose of liposomal irinotecan. *Id.* at 40–41.

The preponderance of the evidence favors Petitioner’s position. Indeed, Bayever teaches treating patients who are homozygous for

UGT1A1*28 allele with 60 mg/m² liposomal irinotecan MM-398, 200 mg/m² of leucovorin or 400 mg/m² of the l+d racemic mixture of leucovorin, and 2,400 mg/m² 5-FU. Ex. 1006, 3, 26–27. In other words, Bayever teaches the combination of three of the four claimed drugs, administered at the claimed doses.

Patent Owner emphasizes that Bayever is “entirely silent on any combination therapy that includes oxaliplatin.” PO Resp. 37; *see also id.* (arguing that both Ko and Saif are also silent on combination therapy that includes oxaliplatin). Petitioner, however, does not rely on Bayever, Ko, or Saif for teaching oxaliplatin. Instead, Petitioner relies on the Conroy references, Mahaseth, and Cantore for that limitation. *See* Pet. 40–41 (claim chart). “[O]ne cannot show non-obviousness by attacking references individually where, as here, the [challenges] are based on combinations of references.” *In re Keller*, 642 F.2d 413, 426 (CCPA 1981).

Thus, we agree with Petitioner that Bayever “disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims along with the exact same claimed doses of leucovorin and 5-FU.” *See* Pet. 42.

c. Reason to Combine

Petitioner argues that a POSA would have been motivated to replace free irinotecan in FOLFIRINOX with liposomal irinotecan in view of Bayever, Ko, and Saif. Pet. 42–43 (citing Ex. 1002 ¶¶ 235–240; Ex. 1007, 1; Ex. 1008, 5).

Patent Owner argues that Petitioner “presents its obviousness argument piecemeal, addressing a single modification at time.” PO Resp. 2; *see also id.* at 24 (same), 32 (“[Petitioner] 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.”), 40 (“[Petitioner] 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.”). We disagree with Patent Owner's analysis.

The Conroy references teach modified FOLFIRINOX that includes reducing oxaliplatin dosage at 60 mg/m² and eliminating bolus 5-FU.²⁰ Ex. 1003, 3; Ex. 1004, 16–18; Ex. 1017, 3–7. Conroy teaches leucovorin at the claimed dosage. Ex. 1003, 3; Ex. 1004, 14. Thus, as explained in the DI, The Conroy references “describe a treatment protocol for some pancreatic cancer patients that differs from claim 1 of the '552 patent solely in the type of irinotecan administered.” DI 35.

Bayever teaches a combination therapy for treating metastatic pancreatic cancer with three of the four claimed drugs (liposomal irinotecan, leucovorin, and 5-FU), administered at the claimed doses. Ex. 1006, 3, 26–27. The only drug Bayever does not disclose is oxaliplatin, which is taught by the Conroy references.

Therefore, Petitioner challenges claim 1 as obvious over a combination of the Conroy references and Bayever: the former differing

²⁰ Petitioner also refers to Mahaseth for teaching a modified FOLFIRINOX regimen with the same claimed dose of 5-FU and leucovorin, which “eliminates the 400 mg/m² bolus while still maintaining an acceptable toxicity profile and superior efficacy over other first-line therapies.” Pet. 43 (citing Ex. 1002 ¶¶ 110–113, 244; Ex. 1005, 1–4). This redundant evidence supplies additional support for Petitioner's argument.

from claim 1 in the type of irinotecan, and the latter silent on oxaliplatin. We are unpersuaded by Patent Owner's argument that Petitioner alleges obviousness in a piecemeal fashion, with "one modification at a time." See PO Resp. 24.

Dr. Ratain testifies that "a POSA would have been motivated to use liposomal irinotecan (MM-398) in place of the free irinotecan in Conroy/FOLFIRINOX." Ex. 1002 ¶ 235. According to Dr. Ratain, "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." *Id.* ¶ 83. Dr. Ratain testifies that

preclinical studies of [liposomal irinotecan] 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.)

Ex. 1002 ¶ 91.

Dr. Ratain's testimony is consistent with the prior art's teachings. Bayever teaches that

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.

Ex. 1006, 9 (emphasis added). Bayever also teaches that “the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy.” *Id.* at 5, 16.

Ko teaches that MM-398 “has been shown in preclinical studies to improve pharmacokinetics and tumour bio-distribution of both irinotecan and its active metabolite SN-38 when compared with the free form of the drug, with less accumulation in many of the target organs associated with toxic side effects.” Ex. 1008, 2. Ko teaches that MM-398 “demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model.” *Id.*

Ko reports that in a phase 2 study, monotherapy liposomal irinotecan “demonstrates moderate antitumour activity with a manageable side effect profile for metastatic, gemcitabine-refractory pancreatic cancer patients.” Ex. 1008, 1. Ko suggests additional studies to explore MM-398’s “potential role in the first-line setting and as part of combination regimens for APC [advanced pancreatic cancer].” *Id.* at 5. Specifically, “given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status,” Ko envisions further investigation of the utility of MM-398 “in

irinotecan-pretreated patients, alone or in combination with gemcitabine.”
Id.

Similarly, Saif suggests evaluating liposomal irinotecan in first-line combination therapy. Ex. 1007, 1. In view of FOLFIRINOX “as an option for first-line treatment,” Saif suggests that it “seems logical” to test “replacing irinotecan in FOLFIRINOX with MM-398.” *Id.*

Thus, the prior art provides specific reasons to replace irinotecan with liposomal irinotecan to treat metastatic pancreatic cancer, and we find such reasons would have motivated the ordinarily skilled artisan to modify the prior art to arrive at the claimed subject matter.²¹ Ex. 1002 ¶¶ 235–240; Ex. 1006, 10; Ex. 1007, 1; Ex. 1008, 2. The asserted prior art reflects “only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from” the disclosure of the ’552 patent. *McLaughlin*, 443 F.2d at 1395. As a result, we do not find Petitioner’s obviousness analysis is hindsight driven.

²¹ Alternatively, the prior art also provides specific reasons to include oxaliplatin in Bayever’s regime. For example, it was known that both free irinotecan and liposomal irinotecan have the same metabolite, SN-38. *See* Ex. 1006, 11; Ex. 1041, 2. It was also known that synergism exist between oxaliplatin and 5-FU, and between oxaliplatin and SN-38. Ex. 1004, 10; Ex. 1041, 2; Ex. 2038, 2. Prior art further teaches the different mechanisms of action and non-overlapping toxicities of oxaliplatin, 5-FU, and irinotecan. Ex. 1041, 2; Ex. 2038, 2. Synergism, different mechanisms of action, and non-overlapping toxicities were the bases for several combination therapies. Ex. 1041, 2; Ex. 2038, 2. Here, it would support a reason to combine the teachings of the Conroy references (combination therapy with oxaliplatin) and Bayever (combination therapy including all the claimed drugs at the claimed dosages, except oxaliplatin).

In sum, on this record, we find Petitioner has shown by a preponderance of the evidence that a POSA would have had a reason to combine the teachings of the Conroy references and Bayever to arrive at the method recited in claim 1.

d. Reasonable Expectation of Success

Petitioner argues that because “the prior art showed each component of the claimed invention had known efficacy in treating pancreatic cancer,” and “because the claimed doses were in known ranges of use and the doses had all been used or proposed, a POSA had a reasonable expectation of success in arriving at the claimed invention.” Reply 15–16. We find Petitioner’s argument persuasive. We address Patent Owner’s counterarguments below.

Patent Owner points to Dr. Oberstein’s testimony that “a POSA would not have expected to maintain efficacy while simultaneously lowering doses of multiple FOLFIRINOX components.” Sur-reply 18 (citing Ex. 2076 ¶¶ 288–93). According to Patent Owner,

A POSA would understand that the effect of [Petitioner] 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.

PO Resp. 48; *see also id.* at 42–43 (arguing that Petitioner “improperly relies on outcomes reported for prior-art regimens to evidence a POSA’s expectations with regard to the claimed multi-drug regimen,” because “the

outcomes reported for Dr. Ratain’s cited references are for treatment regimens different from the claimed invention”).

As an initial matter, we note that Dr. Oberstein testified that the bar for a reasonable expectation of success is higher than that in clinical trials. Ex. 1210, 315:4–12. Dr. Oberstein understood a reasonable expectation of success as a POSA would expect a combination regimen is “more likely than not to provide benefit for the patient compared to the old regimen.” *Id.* at 315:13–25. We find Dr. Oberstein applied an incorrect standard in evaluating reasonable expectation of success.

As Patent Owner acknowledges, the challenged claims do not require a particular level of clinical efficacy. *See* PO Resp. 58 (arguing that Petitioner “identifies no intrinsic support for a claim construction that requires some (unspecified) degree of clinical efficacy”), *id.* n.6 (stating with agreement that “[t]he Board found in its Institution Decision that the ’552 patent claims do not require clinical efficacy”) (citing DI 45). Instead, under our claim construction, the treatment only needs to result in “more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.” DI 14. As such, we disagree with Dr. Oberstein that a POSA would have a reasonable expectation of success only if the result of the treatment is “statistically significant” “in comparison to the other alternatives available to that patient.” *See* Ex. 1210, 351:11–352:7, 355:14–25.

Because Dr. Oberstein applied an incorrect standard in evaluating reasonable expectation of success, we accord little weight to his opinion that a POSA, combining the teachings of the asserted prior art, would not have had a reasonable expectation of success in arriving at the claimed invention.

Reasonable expectation of success “refers to the likelihood of success in combining references to meet the limitations of the claimed invention.” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). As explained above, Petitioner has shown that the asserted prior art teaches combination therapies including each of the four recited drug at the recited doses to effectively treat metastatic pancreatic cancer. *See supra* Section II.G.3.a, 3.b.

Indeed, the Conroy references teach that FOLFIRINOX, including modifications such as reducing oxaliplatin dosage at 60 mg/m² and eliminating bolus 5-FU, “was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status.” Ex. 1003, 3, 6; Ex. 1004, 16–18; Ex. 1017, 3–7; *see also* Ex. 1005, 5 (removing bolus 5-FU from FOLFIRINOX “is well tolerated and has significant activity” in metastatic pancreatic cancer); Ex. 1041, 4 (discussing a modified FOLFIRINOX as first-line therapy with the median starting dose at 80% of that used in Conroy, stating that despite the dose reductions, “the efficacy was maintained”).

Ko teaches liposomal irinotecan has “moderate antitumour activity with a manageable side effect profile” for treating metastatic pancreatic cancer. Ex. 1008, 1. The results of Ko’s clinical trial were “encouraging enough to warrant moving ahead with a larger study in a similar patient population, currently ongoing as an international randomised phase 3 trial called NAPOLI-1.” *Id.* at 5. Saif, with the results of that phase 3 trial, further demonstrates an expectation that substituting liposomal irinotecan for free irinotecan will likely succeed in treating metastatic pancreatic cancer patients. *See* Ex. 1007, 1 (teaching “the combination of MM-398 with

5-fluorouracil (5-FU) and leucovorin 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”).

As explained above, the Conroy references describe a treatment protocol for some pancreatic cancer patients that differs from claim 1 of the ’552 patent solely in the type of irinotecan administered. And Bayever teaches a combination therapy for treating metastatic pancreatic cancer with three of the four claimed drugs (liposomal irinotecan, leucovorin, and 5-FU), administered at the claimed doses. Thus, we are not persuaded by Patent Owner’s argument that “the effect of [Petitioner] CSPC’s multiple, specific modifications to FOLFIRINOX is tantamount to an entirely new combination therapy, composed of different components in different doses.” PO Resp. 48. Instead, we find Petitioner’s obviousness theory is based on a modification of existing treatment regimen that is suggested by the prior art.

Patent Owner also asserts that Petitioner’s alleged “reasonable expectation of success” relies on an erroneous claim construction of “treating.” PO Resp. 45–46 (citing Pet. 26–27, 49–50). We disagree.

Petitioner argues that, because under proper claim construction, claim 1 does not require clinical efficacy,

the bar to proving obviousness of the Challenged Claims is much lower since 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 over the gemcitabine/nab-paclitaxel control arm. As Dr. Ratain explains, methods of treating metastatic pancreatic cancer are always with the hope that the patient will live longer, but that is often not the case. (Ex. 1002, ¶¶49-50.) However, these are still valid methods of treatment because

they are administered for the *purpose* of trying to extend and improve life, not a guarantee that they will. (*Id.*)

Pet. 49–50.

As explained in the DI, the ’552 patent discloses that “patients may or may not receive some therapeutic benefit from the treatment.” DI 13 (citing Ex. 1001, 33:4–9, 40:58–63). Although “the claims do not require that the treatment regimen be superior to any other standard treatment,” Dr. Ratain recognized that “*the POSA would expect that the treatment regimen be superior to no treatment in some regard.*” Ex. 1002 ¶ 49 (emphasis added). Dr. Oberstein offers similar opinions. *See* Ex. 2076 ¶ 139 (“When administering ‘treatment’ to metastatic pancreatic cancer patients, the *goal* is always that such treatment will have more than a *de minimis* therapeutic benefit or efficacy for that patient. While some patients may not receive a therapeutic benefit, the *intention* behind any treatment is for such benefit to occur.”) (emphases added).

We find that Petitioner’s argument on reasonable expectation of success is supported by the testimony of both Dr. Ratain and Dr. Oberstein, and is consistent with the Board’s construction, requiring “treatment” to “have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.”

Patent Owner argues that there would have been no reasonable expectation of success because preclinical and early-phase clinical data are not predicative of successful clinical outcomes. PO Resp. 49. Patent Owner further argues that Petitioner “ignores the unpredictability of clinical effects of the drugs at issue, particularly in combination.” *Id.* This argument is unavailing.

Expectation of success need only be reasonable, not absolute. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (“Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.”). Indeed, “a showing of reasonable expectation of success in a method of treatment claim need not rely on clinical data . . . nor must it include a demonstration of certainty that the treatment would be successful in every instance.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1346 (Fed. Cir. 2021).

Quoting *OSI Pharms., LLC v. Apotex, Inc.*, Patent Owner contends that “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.” PO Resp. 50 (quoting 939 F.3d 1375, 1385 (Fed. Cir. 2019)). The facts in *OSI* are distinguishable from those in this case.

In *OSI*, “the asserted references do not disclose *any* data or other information about [the claimed drug’s] efficacy in treating” the disease. 939 F.3d at 1383. There, the court repeatedly pointed out that “[t]he record does not contain any clinical (human) data or preclinical (animal) data. It does not even include *in vitro* (test tube) data regarding [the claimed drug’s] effect on” the disease.” *Id.*; *see also id.* at 1384 (“These references thus contain no data or other promising information regarding [the claimed drug’s] efficacy in treating [the disease].”), 1385 (“Notably absent from this combination, however, is any data or other information regarding [the claimed drug’s] effect on [the disease].”).

In contrast, here, Petitioner relies on prior art that not only provides *in vitro* and preclinical data, but also data from clinical trials, including phase 3 clinical trial of combination therapy with the claimed drugs in treating metastatic pancreatic cancer.

Moreover, the claim-at-issue in *OSI* recites administering “a therapeutically effective amount of” the claimed drug, which was construed to mean “an amount sufficient to treat the mammal.” 939 F.3d at 1378, 1381. It is undisputed that the challenged claims here do not require clinical efficacy. Therefore, Patent Owner’s reliance on *OSI* is inapposite.

In sum, we find Petitioner has shown, by a preponderance of the evidence, that a POSA, combining the teachings of the asserted prior art, would have had a reasonable expectation of success in arriving at the claimed invention.

e. Unexpected Results

Patent Owner argues that unexpected results support a conclusion of non-obviousness. PO Resp. 50. Patent Owner argues that the differences between the claimed method and the FOLFIRINOX regimen “entail two dose reductions and introduction of a new component.” *Id.* at 52. According to Patent Owner, “[a] POSA would understand that dose reduction of multiple components in a combination therapy may, as a general matter compromise efficacy.” *Id.* (citing Ex. 2076 ¶¶ 263, 288–291, 306–308). Patent Owner contends “[t]hat the claimed methods provide comparable efficacy with an improved toxicity profile was unexpected.” *Id.* (citing Ex. 2076 ¶¶ 303–309); *see also id.* (“Comparable efficacy and improved toxicity profile relative to FOLFIRINOX is a difference in kind, particularly

given the extent of differences between the two regimens.”). We are not persuaded by Patent Owner’s argument.

Evidence of unexpected results is only relevant if there is a nexus between the claimed invention and the objective indicia. *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017). There is no nexus unless the evidence presented is reasonably commensurate with the scope of the claims. *Id.* The patentee bears the burden of showing that a nexus exists. *WMS Gaming Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999).

A patentee is entitled to a rebuttable presumption of nexus between the asserted evidence of unexpected results and a patent claim “when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (quotation marks omitted). “Whether a product is coextensive with the patented invention, and therefore whether a presumption of nexus is appropriate in a given case, is a question of fact.” *Id.*

Patent Owner argues that the record evidence establishes nexus because “the NALIRIFOX regimen comprises the 552 patent’s recited components and doses.” Sur-reply 20 (citing PO Resp. 6–8; Ex. 2076 ¶¶ 65–68). We disagree with Petitioner’s argument.

As an initial matter, we note that when asked if he offered “any opinions about the nexus related to unexpected results and the claims,” Dr. Oberstein testified that “I don’t believe I did that.” Ex. 1210, 380:5–17.

Petitioner points out that “the claims require specific doses of four drugs two weeks apart,” which Petitioner argues is inconsistent with the

NALIRIFOX regimen and data Patent Owner relies on as allegedly showing unexpected results. Reply 21. Petitioner offers evidence to show that

most participants and even more of the long-term survivors experienced dose reductions and delays. (Ex. 1202 (52.5% and 60% of participants—and 66.7% and 80% of long-term survivors—received dose reductions of liposomal irinotecan and oxaliplatin, respectively; 70%-86.7% of participants received dose delays of same); Ex. 1207, 1 (same); Ex. 1201 (same).

Reply 21.

Patent Owner asserts that Petitioner's argument "appears to assume a claim construction that would preclude any modification of the recited doses during the course of treatment." Sur-reply 20. As an example, Patent Owner points to Petitioner's argument that "the claims require specific doses of four drugs two weeks apart." *Id.* (citing Reply 21–22).

Elsewhere, however, Patent Owner appears to agree with Petitioner. Indeed, Patent Owner contends that "claim 1 requires administration of each of the recited drugs in the specifically recited dose for each, once every two weeks." Paper 50, 3. Patent Owner does not sufficiently reconcile that argument with its other argument that "a POSA would understand the recited treatment methods to comprise at least the recited starting dose, with subsequent dose modifications permitted." Sur-reply 20–21.

We agree with Patent Owner that "because the recited antineoplastic therapy must literally 'consist of' the four drugs at the specific four recited doses, administered 'once every two weeks,' deviation from the recited doses within the claimed administration period falls literally outside the scope of claim 1." Paper 50, 5. Therefore, in view of the evidence showing "[d]ose reductions and/or treatment delays occurred in the majority of

long-term survivors,” we find the NALIRIFOX regimen is not coextensive with claim 1. *See* Ex. 1202.

In sum, because Patent Owner is not entitled to the presumption of nexus between its asserted evidence of unexpected results and claim 1,²² and Patent Owner has not otherwise provided persuasive evidence of a nexus between the claimed invention and the alleged unexpected results, we accord little weight to the evidence of unexpected results.

f. Summary

In sum, we find Petitioner has shown, by a preponderance of the evidence, that the combination of the asserted prior art teaches or suggests each limitation of claim 1. Petitioner also has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to combine the teachings the asserted prior art, and in doing so, would have had a reasonable expectation of success to arrive at the claimed invention. In addition, having accorded Patent Owner’s evidence of objective indicia its proper weight, we do not find it outweighs the other *Graham* factors and the evidence of obviousness on this record. As a result, we find Petitioner has shown, by a preponderance of the evidence, that the combination of Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, and Cantore renders claim 1 obvious.

4. Claims 3–6 and 8–14

Petitioner asserts that claims 3–6 and 8–14 would have been obvious over the prior art combination. Pet. 53–58. Patent Owner does not separately

²² Alternatively, even if Patent Owner is entitled to the rebuttable presumption of nexus, we find Petitioner has presented sufficient evidence to rebut that presumption.

argue the patentability of claims 3–6 and 8–14. *See generally* PO Resp.; Sur-reply.

We find persuasive Petitioner’s mapping of the additional limitations of claims 3–6 and 8–14 to the asserted prior art and adopt it as our own. *See* Pet. 53–58. For the same reasons we find Petitioner has shown that claim 1 would have been obvious over the prior art combination, we find Petitioner has shown that claims 3–6 and 8–14 would have been obvious over the combination of Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, and Cantore.

H. Alleged Obviousness of Claims 2, 7, and 15

Petitioner asserts that claims 2, 7, and 15 would have been obvious over the combination of Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, and Ginocchi. Pet. 58–60. After reviewing the entire record developed at trial, and as explained below, we determine Petitioner has not shown by a preponderance of the evidence that the asserted combination of prior art renders claims 2, 7, and 15 obvious.

1. Relevant Prior Art Disclosure

a. Conroy Protocol

In addition to the disclosures discussed above (*see supra* Section II.G.2.b), Conroy Protocol further teaches that “[t]reatment will begin with oxaliplatin 85 mg/m² IV infused over 2 hours, followed by folinic acid 400 mg/m² IV infused over 2 hours and irinotecan 180 mg/m² IV infused over 1.5 hours, to be started immediately after completion of the oxaliplatin infusion.” Ex. 1004, 15.

b. Bayever

In addition to the disclosures discussed above (*see supra* Section II.G.2.e), Bayever further teaches that

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. In a particular embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin.

Ex. 1006, 13.

c. Masi

Masi reports a “phase II study to evaluate the safety and the activity of a simplified biweekly FOLFOXIRI regimen with slightly reduced doses of irinotecan and oxaliplatin and a continuous, rather than chronomodulated, infusion of 5-FU.” Ex. 1012, 2. The patients had unresectable metastatic colorectal cancer. *Id.* at 1. Masi teaches

[t]he treatment planned consisted of: irinotecan 165 mg/m² in 250 ml of NaCl 0.9% over 1 h, followed immediately by oxaliplatin 85 mg/m² in 250 ml dextrose 5% and l-LV 200 mg/m² in 250 ml dextrose 5%, infused concomitantly over 2 h via a Y-connector, followed immediately by 5-FU 3200 mg/m² infused as a 48-h continuous infusion.

Ex. 1012, 3; *see also id.* at 5 (“[W]e studied a three-drug combination of irinotecan, oxaliplatin and 5-FU/LV (FOLFOXIRI) using the treatment sequence irinotecan → oxaliplatin → 5-FU, because an *in vitro* study on two human colon cancer cell lines showed that synergy occurs only when irinotecan precedes oxaliplatin/5-FU exposure.”).

Masi concludes that “this simplified FOLFOXIRI combination has manageable toxic effects and very promising antitumor activity. While the

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

d. Ginocchi

Ginocchi studied “the tolerability and activity of a modified (m) FOLFOXIRI regimen in metastatic or locally advanced pancreatic cancer patients.” Ex. 1016, 1. Ginocchi’s mFOLFOXIRI 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.” *Id.* Ginocchi states that its mFOLFOXIRI regimen was “quite well tolerated and it maintained its good activity in metastatic pancreatic cancer.” *Id.*

2. Claim 2, 7, and 15

Each of claims 2, 7, and 15 depends from claim 1. Claim 2 further recites that “each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.” Claim 7 further requires administering the drugs in the following order: liposomal irinotecan, oxaliplatin, leucovorin, 5-FU. Claim 15 further requires administering oxaliplatin after liposomal irinotecan and administering a corticosteroid and an anti-emetic to the patient before the antineoplastic therapy. The common limitation among claims 2, 7, and 15 is that administration of liposomal irinotecan precedes that of oxaliplatin.

Patent Owner contends that the asserted prior art does not teach or suggest administering liposomal irinotecan before oxaliplatin. PO

Resp. 53–56. For the following reasons, we find Patent Owner’s argument persuasive.

First, Petitioner argues that it would have been obvious to administer liposomal irinotecan first because “Bayever discloses that liposomal irinotecan MM-398 should be administered first before any other drugs.” Pet. 58. Bayever, however, does not include oxaliplatin, and thus, does not teach administering liposomal irinotecan before oxaliplatin. *See* Ex. 1006, 3, 13, 14, claim 4.

Second, as Patent Owner points out, Conroy teaches administering oxaliplatin before irinotecan. PO Resp. 54 (citing Ex. 1003, 3). Other references Petitioner relies on similarly teach administering oxaliplatin before irinotecan in combination therapy. *See, e.g.*, Ex. 1005, 2; Ex. 1009, 2; Ex. 1041, 2 (teaching that “[m]ore cytotoxicity was found in vitro when oxaliplatin was given before SN-38,” the main active metabolite of both free and liposomal irinotecan).

Third, the only prior art that teaches administering irinotecan before oxaliplatin is Masi. Pet. 58 (citing Ex. 1012, 5). Masi, however, developed “a simplified FOLFOXIRI regimen” to treat colon cancer, not pancreatic cancer. Ex. 1012, 1. Although we generally agree that “POSAs would have considered sequencing and suggestions from other cancers” (*see* Reply 17 (citing Ex. 1210, 236:12–237:9)), in this case, Masi suggests the type of cancer plays an important role in the sequence of drug administration.

Indeed, Masi teaches administering irinotecan first because “an *in vitro* study on two human colon cancer cell lines showed that synergy occurs only when irinotecan precedes oxaliplatin/5-FU exposure.” Ex. 1012, 5. Petitioner has not presented evidence to show that similar

synergy would exist in pancreatic cancer cells. In fact, as Patent Owner observes, Masi “predate[s] Conroy and the emergence of FOLFIRINOX as the first-line standard of treatment of metastatic pancreatic cancer by over six years” (*see* PO Resp. 55), yet, Petitioner has not pointed to any prior art teaching administering irinotecan before oxaliplatin in treating pancreatic cancer, or any evidence that suggests a reason to do so. To the contrary, as explained above, references Petitioner relies on teach administering irinotecan after oxaliplatin in treating pancreatic cancer. *See, e.g.*, Ex. 1003, 3; Ex. 1005, 2; Ex. 1009, 2.

Fourth, Petitioner argues that the “claimed order of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients.” Pet. 59 (citing Ex. 1016, 1); *see also id.* at 58 (“Ginocchi applied a modified FOLFOXIRI regimen (which administers the irinotecan before the oxaliplatin) to metastatic pancreatic patients which was shown to be well tolerated with good efficacy.”) (citing Ex. 1016, 1). As Patent Owner points out, however, Ginocchi is silent on the sequence of administration. PO Resp. 55 (citing Ex. 1016, 1).

To the extent Petitioner suggests that Ginocchi’s sequence of administration is the same as Masi’s, Petitioner has not pointed to persuasive evidence to support this argument. Masi teaches “a simplified FOLFOXIRI regimen.” Ex. 1012, 1. Ginocchi teaches “a modified (m) FOLFOXIRI regimen.” Ex. 1016, 1. The two regimens, although similar, are not the same. *Compare* Ex. 1012, 1 (regimen comprising 165 mg/m² irinotecan and 3200 mg/m² 5-FU), *with* Ex. 1016, 1 (regimen comprising 150 mg/m² irinotecan and 2800 mg/m² 5-FU). Petitioner has not shown sufficiently that

despite the different dosages, the two regimens employed the same sequence of administration.

Because Petitioner has not met its burden to show that a POSA would have administered liposomal irinotecan before oxaliplatin in treating metastatic pancreatic cancer, we determine Petitioner has not shown by a preponderance of the evidence that the asserted combination of prior art renders claims 2, 7, and 15 obvious.

We find Petitioner has not shown obviousness of claim 2 for another reason. Petitioner argues that, although the asserted references “do not explicitly mention that oxaliplatin be administered 2 hours after liposomal irinotecan, this would have been merely routine optimization to determine this variable.” Pet. 59. But, as Patent Owner points out, Dr. Ratain did not opine on claim 2. *See* PO Resp. 53 (citing Ex. 1002 ¶¶ 308–311; Ex. 2073, 22:12–20). Because Petitioner cites no evidence for support, we are not persuaded by its attorney argument on routine optimization.

In the Reply, Petitioner further contends that the two-hour spacing interval reflects a need to flush the infusion line between drugs “to mitigate acute overlapping toxicities and line-compatibility constraints.” Reply 18 (citing Ex. 1038, 2, 4). According to Petitioner, the fact that “there is no evidence of criticality for the claimed interval” confirms the two-hour spacing interval is an “obvious design choice.” *Id.* We are not persuaded by this argument either.

Exhibit 1038 teaches that because oxaliplatin “is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil),” the infusion line should be flushed in before administration of any concomitant medication. Ex. 1038, 4. Claim 2, however, requires

administering liposomal irinotecan two hours before oxaliplatin. Petitioner provides no evidence to show that liposomal irinotecan is incompatible with oxaliplatin.

In sum, Petitioner relies solely on unsupported attorney argument to address the two-hour spacing interval recited in claim 2. For this additional reason, we determine Petitioner has not shown by a preponderance of the evidence that the asserted combination of prior art renders claim 2 obvious.

I. Alleged Obviousness of Claims 1–15

Petitioner asserts that claims 1–15 would have been obvious over the combination of Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi, Carnevale, and Dean. Pet. 60–63.

Petitioner presents this ground as an alternative to the other two challenges discussed above, with the premise that the priority date is November 10, 2017. Pet. 60. As explained above, we determine the challenged claims are entitled to the priority date of August 21, 2015. *See supra* Section II.D. As a result, we find it unnecessary to reach this ground.²³

III. MOTION TO SEAL

Petitioner filed a Motion to Seal, seeking to seal Exhibit 1210 and the Reply. Paper 31, 1. Petitioner represents that the parties “have agreed that Exhibit 1210 and the Reply should be filed under seal.” *Id.* at 2.

The record of an *inter partes* review shall be made available to the public, except as otherwise ordered, and a document filed with a motion to seal shall be treated as sealed until the motion is decided.

²³ Even if reached, this ground would have the same shortcomings as the other ground for claims 2, 7, and 15.

35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Only “confidential information” may be protected against public disclosure. 35 U.S.C. § 316(a)(7); 37 C.F.R. § 42.54. The standard for granting a motion to seal is “good cause.” 37 C.F.R. § 42.54(a). The moving party bears the burden of showing that the relief requested should be granted. 37 C.F.R. § 42.20(c).

Exhibit 1210 is the deposition transcript of Patent Owner’s declarant, Dr. Paul Oberstein. Petitioner states that “Patent Owner has designated portions of the transcript as confidential.” Paper 31, 1. According to Petitioner, “the parties do agree that Exhibit 1210 does contain confidential financial information for Dr. Oberstein.” *Id.* Because the Reply contains that confidential information, Petitioner also moves to seal the Reply. *Id.* Petitioner filed redacted versions of Exhibit 1210 and the Reply (Paper 33).

Upon review of Exhibit 1210 and the Reply, we are persuaded that good cause exists to seal the redacted portions because they contain Dr. Oberstein’s confidential financial information. We, therefore, grant Petitioner’s Motion to Seal.

IV. CONCLUSION²⁴

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has demonstrated by a

²⁴ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner’s attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any

preponderance of the evidence that claims 1, 3–6, and 8–14 of the '552 patent would have been obvious. We, however, find Petitioner has not met its burden to show that claims 2, 7, and 15 are unpatentable.

In summary:

Claims	35 U.S.C. §	References	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 3–6, 8–14	103	Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore	1, 3–6, 8–14	
2, 7, 15	103	Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi		2, 7, 15
1–15 ²⁵	103	Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi, Carnevale, Dean		
Overall Outcome			1, 3–6, 8–14	2, 7, 15

such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

²⁵ As explained above, because this challenge is premised on a priority date that we do not adopt, we do not reach this ground. *See supra* Section II.I.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has shown, by a preponderance of the evidence, that claims 1, 3–6, and 8–14 of the '552 patent are unpatentable;

FURTHER ORDERED that Petitioner has not shown, by a preponderance of the evidence, that claims 2, 7, and 15 of the '552 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Seal (Paper 31) is granted;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 43) is denied;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 42) is denied; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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