IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANOFI-AVENTIS U.S. LLC and SANOFI MATURE IP, Plaintiffs v. SANDOZ, INC., Defendant.	Civil Action No. 20-804-RGA CONSOLIDATED

TRIAL OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Sanofi-Aventis and Sanofi Mature IP brought this patent infringement action under 35 U.S.C. §§ 271(e)(2)(A) & 271(b) against Defendant Sandoz. (D.I. 1 ¶ 2). I held a three-day bench trial from January 11 to 13, 2023. The parties narrowed the issues to infringement and invalidity for obviousness of four claims of a single patent, U.S. Patent No. 10,716,777 ("the '777 patent").

For the following reasons, I find the asserted claims of the '777 patent infringed and not invalid for obviousness.

I. BACKGROUND

Plaintiff Sanofi-Aventis holds New Drug Application ("NDA") No. 201023 for JEVTANA®, which was approved by the Food and Drug Administration (FDA) in 2010. (D.I. 328-1 Ex. 1 ¶ 17). JEVTANA® is used "in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen." (*Id.* ¶ 18). The active ingredient of JEVTANA® is cabazitaxel. (*Id.* ¶ 19). The '777 patent is listed in the FDA's Orange Book for JEVTANA®. (*Id.* ¶ 20). The '777 patent claims methods of "increasing survival" in patients with metastatic castration resistant prostate cancer "that has progressed during or after treatment with docetaxel." ('777 patent at 18:54, 60-61).

Metastatic castration-resistant prostate cancer (mCRPC) is prostate cancer that has spread beyond the prostate and has become resistant to the hormonal therapies used as a first line of defense. (D.I. 350 ¶ 6, D.I. 352 ¶ 31). Both cabazitaxel and docetaxel belong to a class of chemotherapy drugs called taxanes and share a mechanism of action. (Tr. at 71:4-6, 73:17-24,

241:4-11). [1] Docetaxel was developed earlier than cabazitaxel and used to treat mCRPC. (D.I. 350 ¶ 7, D.I. 352 ¶ 40; Tr. at 71:13-72:3, 151:2-20, 242:1-14). Some patients would eventually develop a resistance to docetaxel, which is referred to as being "docetaxel-refractory." (D.I. 350 ¶ 8, D.I. 352 ¶ 41; Tr. at 243:21-244:4). A patient that has not yet developed resistance is "docetaxel-sensitive." (Tr. at 244:5-16).

Prior to the development of cabazitaxel, some docetaxel-refractory patients were treated with a non-taxane chemotherapy drug, mitoxantrone. (Tr. at 73:7-14, 240:4-25). A 25 mg/m^2 dose of cabazitaxel was shown in the 2010 TROPIC trial to improve survival in docetaxel-refractory patients relative to mitoxantrone. (JTX-012 at 1147; Tr. at 75:10-17, 162:11-14). JEVTANA® was approved based on the TROPIC trial. (Tr. at 73:25-74:5). In the PROSELICA trial, conducted after JEVTANA®'s approval, patients treated with a 20 mg/m^2 dose of cabazitaxel were shown to have an overall survival no worse than that of patients treated with a 25 mg/m^2 dose. (JTX-32 at 3198).

Defendant Sandoz filed NDA No. 208715 ("the B2 NDA") under 21 U.S.C. § 355(b)(2) (section 505(b)(2) of the Food, Drug, and Cosmetic Act) for a version of JEVTANA®. (D.I. 328-1 Ex. 1 ¶ 21). The active ingredient in Defendant's product is cabazitaxel at a dose of 20 mg/m^2. (*Id.* ¶ 26; DTX-2273.4). Sandoz received final approval for the B2 NDA on January 5, 2023. (D.I. 335).

II. LEGAL STANDARDS

A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any

[1] The transcript is available at D.I. 345-347. It is consecutively paginated.

patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case such as this, the plaintiff's infringement claim is based on the accused infringer's future conduct, rather than past acts of infringement. Under § 271(e)(2), the "infringement inquiry . . . is focused on the product that is likely to be sold following FDA approval." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."[2] *Id.*

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a claim of induced infringement, the plaintiff must show (1) "that there has been direct infringement," and (2) "that the alleged infringer knowingly induced infringement and possessed

[2] In the present case, the infringement arises from the filing of an NDA under 21 U.S.C. § 355(b)(2), rather than an ANDA under 21 U.S.C. § 355(j), but the law of infringement and induced infringement is no different. *See generally Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 629-31 (Fed. Cir. 2015)

specific intent to encourage another's infringement." *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (internal citation omitted).'

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted claims]." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018). For method-of-treatment patents, if an ANDA applicant's "proposed label instructs users to perform the patented method[,] . . . the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). In that setting, the Federal Circuit has explained, "The label must encourage, recommend, or promote infringement." *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). Evidence that a proposed label will "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of specific intent to induce infringement. *AstraZeneca*, 633 F.3d at 1060.

B. Invalidity

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). "As patents are presumed valid, a defendant bears the burden of proving invalidity by clear and convincing evidence." *Shire, LLC v. Amneal Pharms., LLC*, 800 F.3d 1301, 1306 (Fed. Cir. 2015) (citations omitted). "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against

this background, the obviousness or nonobviousness of the subject matter is determined." *KSR*, 550 U.S. at 406 (internal citation and quotation marks omitted). "For a patent to be obvious, 'some kind of motivation must be shown . . . so that the jury can understand why a person of ordinary skill would have thought of either combining two or more references or modifying one to achieve the patented method.'" *Shire*, 802 F.3d at 1306 (quoting *Innogenetics, N.V. v. Abbott Lab'ys.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008)). In addition to such as motivation, "[a] party seeking to invalidate a patent on the basis of obviousness must 'demonstrate by clear and convincing evidence that . . . the skilled artisan would have had a reasonable expectation of success in doing so.'" *Kinetic Concept, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) (quoting *Procter & Gamble Co. v. Teva Pharm, USA, Inc.*, 566 F.3d 989, 1014 (Fed. Cir. 2009)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

III. DISCUSSION

A. The Asserted Claims

The claims at issue are claims 1, 2, 4, and 5 of the '777 patent. Claim 1 is an independent claim. Claims 2 and 4 depend on claim 1, while claim 5 depends on claim 4. All are method of treatment claims for mCRPC. The claims read,

> 1. A method of increasing survival comprising administering to a patient in need thereof a dose of 20 to 25 mg/m^2 of cabazitaxel, or a hydrate or solvate thereof, in combination with an H_2 antagonist, wherein the H_2 antagonist is administered to the patient prior to administering the dose of cabazitaxel, and wherein said patient has castration resistant metastatic prostate cancer that has progressed during or after treatment with docetaxel.
> 2. The method of claim 1, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2.
> . . .
> 4. The method of claim 1, where the H_2 antagonist is administered at least 30 minutes prior to administering the dose of cabazitaxel.
> 5. The method of claim 4, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2.

('777 patent at 18:54-64, 19:1-6).

I adopted the parties' agreed upon construction of the term "castration resistant metastatic prostate cancer that has progressed during or after treatment with docetaxel," which was, "castration resistant metastatic prostate cancer that has worsened during or after treatment with docetaxel." (D.I. 291).

I likewise adopted the parties' agreed upon construction of the limiting preamble, "A method of increasing survival . . . to a patient in need thereof." That construction is, "A method of increasing survival with the intentional purpose of increasing such survival in an individual patient in need of such a method of increasing survival."[3] (*Id.*).

I construed "increasing survival" to mean "increasing any of: overall survival, tumor progression-free survival, pain progression-free survival, or prostate specific antigen (PSA) progression-free survival, as compared to any other treatment that may be available to the patient (including no treatment)." (D.I. 286, 291)

[3] Left to my own devices, I would have chosen a wording less redundant than "intentional purpose." However, the parties agreed to this construction, and they also seem to agree that "neither party's position turns on the presence of the word 'intentional.'" (D.I. 355 at 1 n.1).

On both infringement and invalidity, the parties present the same arguments for each of the four asserted claims. Therefore, my analysis below does not rely on or refer to any of the distinctions between the asserted claims.

B. Infringement of the '777 Patent

1. Findings of Fact Related to Disputed Issues

1. A person of ordinary skill in the art ("POSA") for purposes of the '777 patent is an individual with an M.D. specializing in hematology/oncology medicine and having several years of experience treating patients with hematology/oncology diseases, including metastatic castration-resistant prostate cancer, and working knowledge of clinical study design and interpretation.[4] (D.I. 352 ¶ 49; Tr. at 236:17-25).

2. Defendant Sandoz has the requisite knowledge of the '777 patent. (D.I. 350 ¶¶ 16-20).[5]

3. Healthcare providers' treatment decisions are primarily driven by weighing the benefits vs. the risks of a particular therapy. (Tr. at 87:11-24, 153:3-9, 165:14-21). Healthcare providers will read Sandoz's entire label to understand the benefits of Sandoz's product. (Tr. at 78:17-79:2, 158:21-159:3, 181:24-182:4).

4. Healthcare providers will review the available clinical data in the Clinical Studies section of Sandoz's label to determine the specific benefits of cabazitaxel treatment, regardless of whether other sections cross-reference it. (Tr. at 88:19-24).

5. The benefit information provided in the Clinical Studies section of Sandoz's label is overall survival data from the PROSELICA study, which investigated the non-inferiority with respect to overall survival of the 20 mg/m^2 dose compared to the 25 mg/m^2 dose. (Tr. at 88:19-89:7, 182:17-183:9; DTX-2273.19-20). Sandoz's label states that "overall survival" was "the major efficacy outcome" of PROSELICA. (Tr. at 88:19-89:7, 185:1-5; DTX-2273.19).

6. Healthcare providers understand that a non-inferiority study has two arms in which patients are enrolled: an active control arm in which patients are treated with a therapy with known benefit, and a comparator arm in which patients are

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[4] The parties agree that neither the infringement nor the invalidity analyses differ depending on which party's definition of a POSA I adopt. (D.I. 350 ¶ 15, D.I. 352 ¶ 51, D.I. 359 ¶ 3; Tr. 237:4-7, 149:16-18). I adopt Defendant's definition, but I note that adopting Plaintiff's definition instead would not change my conclusions.

[5] Defendant does not seem to dispute Plaintiffs' proposed findings of fact regarding Defendant's knowledge.

treated with a different therapy, formulation, or dose. (Tr. at 76:8-16, 90:17-91:2). The outcomes of the two arms are compared to determine whether the patients in the comparator arm did no worse than the patients in the active control arm with respect to the specified beneficial effect, within some statistical margin. (Tr. at 76:8-16, 90:17-91:2).

7. A healthcare provider would infer from the label that some prior study must have collected data on overall survival of patients at the 25 mg/m^2 dose used in the active control arm in order for that dose to serve as an active control. (Tr. at 90:2-11, 183:10-16). A healthcare provider would know that, for the PROSELICA study to have been ethical, the previous overall survival data must have indicated a survival advantage with respect to some other treatment or no treatment. (Tr. at 90:11-91:7, 183:22-184:25).

8. Sandoz's label does not contain any data regarding pain relief, functional status improvement, or any other potential treatment goals outside of overall survival for mCRPC patients. (Tr. at 93:13-24, 132:19-133:11, 190:24-191:8).

9. A healthcare provider reading Sandoz's label would be encouraged to administer cabazitaxel with the intent of increasing patients' survival, rather than for any other purpose. (Tr. at 91:20-92:5)

2. Conclusions of Law

a. FDA Guidance

First, I address the issue of judicial notice. Defendant asks me to take judicial notice of an FDA guidance on the design of non-inferiority studies. (D.I. 355 at 3). Plaintiffs object that Defendant has never raised or cited to this guidance before, and I should not give the guidance weight without supporting expert testimony. (D.I. 362 at 4 & n.3). Plaintiffs also assert that the guidance is "entirely consistent" with their evidence. (*Id.* at 4).

Defendant cites the guidance for three assertions: first, that a non-inferiority study cannot be fully interpreted in isolation (D.I. 355 at 14); second, that a non-inferiority study only requires the comparator arm to perform within a pre-specified margin of the active control on a particular metric (*id.* at 15); and third, that a non-inferiority study may use a different endpoint from the endpoint used in the original trials of an active control (*id.*).

The first assertion follows from both experts' explanations of a non-inferiority study. Plaintiffs' expert, Dr. Peter Nelson, explained that a non-inferiority study seeks only to demonstrate that one dose "was not worse" than another. (Tr. at 76:8-12). Defendant's expert, Dr. Walter Stadler, testified that PROSELICA "compares two separate doses of the same drug." (*Id.* at 171:6-14). Given this information, it is fairly clear that fully interpreting a non-inferiority study depends on some outside understanding of the drug's performance.

The second assertion was explicitly testified to by Dr. Nelson. Dr. Nelson explained that the non-inferiority result merely means that the comparator arm is "[s]tatistically . . . not worse." (*Id.* at 130:15-21). Dr. Nelson acknowledged that the comparator arm in PROSELICA had a different median outcome than the active control. (*Id.* at 129:22-130:14).

The third assertion follows logically from Dr. Stadler's testimony that a POSA might not know the primary endpoint of the original study on the active control. (*Id.* at 183:10-184:3). If a non-inferiority study necessarily used the same endpoint as the original study, a POSA would not be unsure.

Because each assertion supported by the guidance is independently supported by expert testimony, my taking judicial notice of the guidance would not add anything of significance to the record. While the guidance might provide additional corroboration for the experts' assertions, the experts did not seem to disagree on any of these issues. Indeed, I find their testimony on these points to be credible. Thus, I agree with Plaintiffs that the guidance does not contradict any evidence Plaintiffs presented. I do not think the guidance adds any information that would materially change my findings of fact or conclusions of law, other than allowing me to cite an additional source. Therefore, I will disregard the guidance and will not address the amount of

weight that should be given to an administrative guidance raised for the first time in post-trial briefing.

b. Specific Intent to Induce Infringement

The parties' only other dispute with respect to infringement is whether Defendant's product label demonstrates a specific intent to induce infringement of the claim limitation that cabazitaxel be administered with the "intentional purpose" of increasing survival. (D.I. 349 at 6-7, D.I. 355 at 5). The other claim limitations are not disputed (*see id.* at 6-8, D.I. 355 at 2), nor is Defendant's knowledge of the patent. (*Id.* at 5-6; *see generally,* D.I. 355). The parties agree that, as a legal matter, a label that "encourages" or "instructs" users to administer cabazitaxel with the intentional purpose of increasing survival is evidence of specific intent. (D.I. 349 at 5, D.I. 355 at 5). For the reasons below, I think that Defendant's label does encourage healthcare providers to administer cabazitaxel with the intentional purpose of increasing survival. Therefore, I find that Defendant's label demonstrates a specific intent to induce infringement of the '777 patent.

Plaintiffs observe that the label discusses PROSELICA, a clinical trial that used "overall survival" as an endpoint and does not discuss any other possible therapeutic benefits of cabazitaxel. (D.I. 349 at 12, 16). Plaintiffs argue that the label therefore encourages healthcare providers to give cabazitaxel to patients with the intentional purpose of increasing their overall survival. (D.I. 349 at 16). Overall survival is one of the metrics included in my construction of "increasing survival." (D.I. 286, 291). Plaintiffs contend that because the label states that "overall survival" was the "major efficacy outcome" of PROSELICA (DTX-2273.19), medical practitioners will infer that the 20 mg/m^2 dose of cabazitaxel evaluated in that study can be used to "increase overall survival as compared to no treatment or another treatment." (D.I. 349 at 12).

In line with this, Dr. Nelson testified that a healthcare provider reading the label's description of PROSELICA would understand that the overall survival of patients treated with 20 mg/m^2 of cabazitaxel was no worse than that of patients treated with 25 mg/m^2. (Tr. at 91:8-19). Dr. Nelson further testified that a healthcare provider would infer from the disclosures about PROSELICA that 25 mg/m^2 of cabazitaxel had previously demonstrated an overall survival advantage relative to another treatment or no treatment, because it would otherwise have been "impossible to enroll [the] number of patients" that were enrolled. (*Id.* at 90:2-91:7). Dr. Nelson testified that providers would consequently expect 20 mg/m^2 of cabazitaxel to likewise increase their patients' overall survival. (*Id.* at 91:13-19). Therefore, according to Dr. Nelson, providers would understand increasing survival to be the primary benefit of cabazitaxel. (*Id.* at 88:19-89:7).

Plaintiffs note that the PROSELICA information is particularly strong encouragement because Defendant's label does not include information about any other possible benefits. (D.I. 349 at 16-17). Dr. Nelson indicated that "when [a healthcare provider] look[s] at this label in totality with respect to the potential toxicities and side effects . . . the main reason to use this is with the intended purpose of extending a patient's life." (Tr. at 91:20-92:5). Plaintiffs argue that healthcare providers would read the label's omissions as encouraging the use of cabazitaxel specifically for increasing survival, rather than for any other purpose. (D.I. 349 at 17). Plaintiffs argue that this encouragement of the infringing use over other uses strengthens the inference of specific intent. (*Id.* at 17).

Defendant offers four responses. First, Defendant argues that its product is indicated not for increasing mCRPC patients' survival, but "for the treatment" of patients with mCRPC. (D.I. 355 at 5). Dr. Stadler testified that treatment may include increasing the various metrics of

survival but also includes a number of other goals, such as pain relief. (Tr. at 159:15-21). Thus, a practitioner might treat a patient without intending to increase their survival. Dr. Nelson agreed. (*Id.* at 119:20-25). Defendant observes that the indication on a label, while not dispositive, is "key" to the inducement analysis. (D.I. 355 at 5). Defendant cites to *Grunenthal GmbH v. Alkem Labs. Ltd.* to support the argument that inducement cannot rest purely on the fact that a patented method is encompassed by a broader indication. (*Id.* at 11 (citing *Grunenthal*, 919 F.3d 1333, 1339 (Fed. Cir. 2019))). Defendant notes that the District Court reached a similar conclusion in *Vanda Pharms., Inc. v. Teva Pharms. USA, Inc.*. 2022 WL 17593282, at *7 (D. Del. Dec. 13, 2022).

Second, Defendant argues that where its label does mention "survival," it is not referring to "increasing survival" as it is used in the '777 patent, because "increasing survival," as I have construed it, requires that the increased survival be measured relative to another treatment or no treatment. (D.I. 355 at 7). Defendant argues that its label only provides the information that 20 mg/m^2 of cabazitaxel does not worsen overall survival relative to 25 mg/m^2 of cabazitaxel. (*Id.* 355 at 14-16). Thus, it does not support the conclusion that 20 mg/m^2 increases survival relative to 25 mg/m^2. More importantly, the label never compares the survival outcomes of patients treated with 20 mg/m^2 of cabazitaxel to the survival outcomes of patients who received any other course of treatment or no treatment. (*Id.* at 7). In fact, as Dr. Stadler testified, the label does not even state that 25 mg/m^2 increases survival relative to another treatment or no treatment. (*Id.* at 7; Tr. at 161:3-5). Defendant asserts that "inducement cannot rest on inferences about material outside the label." (D.I. 355 at 9 (citing *Takeda*, 785 F.3d at 627-28)). Defendant argues that a practitioner would have to look outside the label to conclude that the 20 mg/m^2 dose increases survival relative to another treatment or no treatment. Because the label lacks any explicit,

affirmative encouragement, Defendant argues that the label cannot induce infringement. (D.I. 355 at 10).

Third, Defendant contends that in addition to the overall survival results of the PROSELICA trial, its label does discuss other outcomes in two places. First, it argues that the label discusses tumor responses in the "Pediatric Use" section. (*Id.* at 18). The "Pediatric Use" section discusses a study in which a patient had a "partial response"—a tumor size metric not included in my construction of "increasing survival." (DTX-2273.14). Thus, Defendant argues, a healthcare provider would "understand that 'increasing survival' was not the only benefit contemplated." (D.I. 355 at 19). Second, it argues that because the label describes cabazitaxel as a taxane and a microtubule inhibitor, both well-known classes of chemotherapy drugs, healthcare providers would understand that cabazitaxel must, like other members of those classes, have benefits beyond overall survival. (*Id.* at 19).

Fourth, Defendant argues that the fact that it actively removed information about the TROPIC trial from its label is also evidence that it lacks the specific intent to induce infringement of that limitation. (*Id.* at 20). Defendant notes that other district courts have considered ANDA defendants' removal of language from its label to be evidence that weighed against finding specific intent. (*Id.* at 20 (citing *In re Depomed Patent Litigation*, 2016 WL 7163647 at *61 (D.N.J. Sept. 30, 2016); *Otsuka Pharm. Co. v. Torrent Pharms. Ltd.*, 99 F. Supp. 3d 461, 485 (D.N.J. 2015))).

I agree with Plaintiffs that Defendant's label encourages, promotes, and recommends the use of cabazitaxel for increasing survival in mCRPC patients. I find Dr. Nelson's description of how a user would interpret the label compelling and credible. Healthcare providers looking at the label would see that cabazitaxel is indicated to treat a given disease and would find that the only

clinical outcome described with any specificity on the label is "overall survival." It makes sense that they would then conclude that the drug is used primarily to increase overall survival, even though it may have additional benefits that fall under the broader umbrella of "treatment." As Defendant itself pointed out, a healthcare provider would understand that as a taxane and microtubule inhibitor, cabazitaxel could be expected to have other benefits, allowing it to be indicated for "treatment." Based on the label, however, I think a healthcare provider would conclude that increases in overall survival were the primary benefit.

As to Defendant's first argument in response, even though Defendant's product is indicated for broader purposes than what is claimed in the '777 patent, Defendant still encourages the patented use in other places in its label. Defendant does not dispute that the inducement analysis is not limited to the "Indications and Usage" section of the label. (D.I. 355 at 5). If treatment is as broad a term as Defendant argues, it seems to me that a healthcare provider would be even more motivated to read the rest of the label to understand the specific benefits the drug has been shown to have. As Dr. Nelson testified, a healthcare provider would not give a toxic drug to a patient with the promise of some unspecified, unknown benefit. (Tr. at 88:13-18). Thus, I do not think the vague language of the Indications and Usage section can help Defendant avoid a finding of induced infringement.

Grunenthal likewise does not help Defendant. First, to the extent that Defendant uses *Grunenthal* to argue that induced infringement "cannot rest on the mere fact that a claimed method is a subset of an indication on a label," (D.I. 355 at 11), Plaintiffs' inducement argument rests on much more than that. Second, the facts of *Grunenthal* are readily distinguishable. In *Grunenthal*, the patent at issue covered a method of treatment for polyneuropathic pain, a specific type of chronic pain. *Grunenthal*, 919 F.3d at 1338. The ANDA reference product was

indicated broadly for chronic pain but also for "neuropathic pain associated with diabetic peripheral neuropathy (DPN)." *Id.* The latter is a type of polyneuropathic pain. The ANDA filers, meanwhile, pursued broad indications, such as "moderate to severe chronic pain," that did not mention DPN, polyneuropathic pain, or even neuropathic pain. *Id.* at 1339. In fact, their labels appear not to have mentioned DPN at all. *Id.* at 1339-40. Similarly, in *Vanda*, the label never discussed the infringing use. 2012 WL 17593282 at *51. Here, Defendant is pursuing an indication identical to Plaintiffs', and its label explicitly discusses overall survival.

As to its second argument, Defendant may be correct that a skeptical healthcare provider reading the label could not be absolutely certain that the 20 mg/m^2 dose had been clinically shown to increase survival relative to another treatment or no treatment. However, the label induces infringement if it encourages a healthcare provider to use the product in an infringing manner, a distinct inquiry. I think that a healthcare provider reading the label would be encouraged by its contents to administer cabazitaxel in order to increase overall survival, regardless of whether the provider could be certain that cabazitaxel had been shown to increase survival without looking up the study. As Dr. Nelson explained, a healthcare provider would search the label for information about the specific benefits of cabazitaxel and would only find information about overall survival.

Unlike cases in which the absence of explicit encouragement of the infringing use is accompanied by encouragement of another specific use, Defendant's label presents overall survival as the only documented benefit. In *Takeda*, for example, the drug in question was both prophylactic and therapeutic, but only therapeutic uses were infringing. 785 F.3d at 629. The court found that a generic indicated only for prophylaxis, supported by only prophylactic data, that encouraged patients to "tell [their] doctor" about acute symptoms did not induce

infringement. *Id.* at 632. Defendant's label has no information about an alternative use, akin to prophylaxis is *Takeda*, other than the vague mention of "treatment" in the indication. Defendant's label provides no further discussion of what "treatment" might be or what benefits it might confer to the patient. A healthcare provider would reasonably conclude that "increasing survival" was the primary intended use of cabazitaxel.

As to Defendant's third argument, Plaintiffs note that the argument about other described benefits of cabazitaxel has never been raised before and is therefore waived. (D.I. 362 at 8 n.5). I think the argument is likely waived, but in any case, I find it unpersuasive. I do not think the passing mention of a "partial response" in the "Pediatric Use" section of the label supports Defendant's assertion that its label suggests using cabazitaxel for other purposes. The "Pediatric Use" section opens with, "The safety and effectiveness of Cabazitaxel Injection in pediatric patients have not been established." (DTX-2273.14). The section also states that the pediatric patients in question had "glioma" or "ependyoma," which are different types of cancers from mCRPC. (DTX-2273.14). I do not think a single pediatric patient—in a small study, on a different cancer, for a drug not approved for pediatric use—would change how healthcare providers understood the primary benefit of cabazitaxel. I also do not think the description of cabazitaxel as a "taxane" and "microtubule inhibitor" provides a practitioner any encouragement to administer cabazitaxel for a purpose other than increasing survival, whether or not those descriptors suggest other possible benefits.

As to Defendant's final argument, I am hesitant to find that the act of removing information when prompted by the FDA is in itself a way to disprove intent. In *Otsuka*, the reference product was indicated for "adjunctive treatment for major depressive disorder," and the proposed generic labels did not include that indication. *Otsuka*, 99 F. Supp. 3d at 485-86. The

court called this "actively and voluntarily" removing the infringing indication and held that it "negate[d] any reasonable inference of an active intent to induce infringement." *Id.* at 485. Similarly, the defendants in *In re Depomed* removed the infringing indication. *In re Depomed*, 2016 WL 7163647 at *61. In the present case, however, Defendant left the indication unchanged from that of the brand-name drug—it merely removed certain clinical data. Moreover, it removed that clinical data to avoid regulatory exclusivity over the 25 mg/m^2 dose, not to avoid infringement and not to change the product's indication. (Tr. at 163:1-24). In fact, given that the FDA suggested the removal of the 25 mg/m^2 dose, calling the removal "voluntary" seems to be an exaggeration. (DTX-2055; Tr. at 163:8-24). I conclude that any weight Defendant's removal of the TROPIC trial carries does not negate the substantial evidence of intent.

On the whole, I find that a healthcare provider reading Defendant's label would be encouraged to administer cabazitaxel for the specific purpose of increasing a patient's survival. It seems to me that a healthcare provider reading Defendant's label would not think to administer cabazitaxel with any other purpose. Therefore, I find that Plaintiffs have proven by a preponderance of the evidence that Defendant's label will induce infringement of the asserted claims of the '777 patent.

C. Invalidity of the '777 Patent

1. Findings of Fact Related to Disputed Issues

1. The priority date for purposes of evaluating what constitutes prior art to the '777 patent is October 29, 2009. (D.I. 331 ¶ 1).

2. The asserted claims of the '777 patent are method of treatment claims that concern administering cabazitaxel with an H_2 antagonist premedication for the intentional purpose of increasing patients' survival.

3. Alain C. Mita et al., *Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors*, 15 Cancer Therapy: Clinical 2, 723 (2009) ("Mita") is prior art to the '777 patent under 35 U.S.C. § 102(b). (JTX-48 at 723).

Mita reports the results of a Phase I clinical trial of cabazitaxel in patients with a variety of advanced solid tumors. (*Id.* at 723-24).

4. The Mita study enrolled 25 patients. (JTX-48 at 723; Tr. at 270:13-14, 374:21-375:1). Of those, eight had prostate cancer. (JTX-48 at 725; Tr. at 270:15-16, 375:2-4). Two of those patients had confirmed partial responses to cabazitaxel, indicating that their tumors shrank. (JTX-48 at 723; Tr. at 273:11-274:16). One of the two had previously been treated with docetaxel and was docetaxel-refractory (Tr. at 274:23-275:4). The other had not been treated with docetaxel. (*Id.* at 278:15-24).

5. Mita also discusses promising preclinical testing of cabazitaxel. (JTX-48 at 723-24; Tr. at 269:14-270:3).

6. A POSA reading the Mita study would conclude that cabazitaxel warrants further evaluation. (Tr. at 282:21-283:1).

7. Gerhardt Attard et al., *Update on tubulin-binding agents*, 54 Pathologie Biologie 2, 72 (2006) ("Attard") is prior art to the '777 patent under 35 U.S.C. § 102(b). (JTX-26 at CabRef0002391). Attard is a review article on tubulin-binding agents, a class of drugs to which taxanes belong. (*Id.*). Attard discusses the results of Mita and concludes that those results suggested that cabazitaxel "may overcome some forms of paclitaxel tumour resistance." (*Id.* at CabRef0002394). Paclitaxel, like docetaxel and cabazitaxel, is a taxane, though it is not used to treat prostate cancer. (Tr. at 12:12-25).

8. X. Pivot et al., *A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients*, 19 Annals Oncology 9, 1547 (2008) ("Pivot") is prior art to the '777 patent under 35 U.S.C. § 102(b). (JTX-55 at CabRef0002984). Pivot reports the results of a Phase II clinical trial of cabazitaxel in seventy-one metastatic breast cancer patients, forty-six of whom had been previously treated with docetaxel. (JTX-55 at CabRef0002984; Tr. at 288:13-15).

9. Pivot reported that ten patients responded to cabazitaxel, two of whom had a complete response. (Tr. at 288:20-25). A POSA reading Pivot would conclude that cabazitaxel appears to be active in taxane-resistant breast cancer. (Tr. at 289:13-19).

10. Emma K. Beardsley and Kim N. Chi, *Systemic therapy after first-line docetaxel in metastatic castration-resistant prostate cancer*, 2 Current Op. Supportive and Palliative Care 3, 161 (2008) ("Beardsley") is prior art to the '777 patent under 35 U.S.C. § 102(b). (JTX-27 at CabRef0002404). Beardsley is a review article discussing treatment options after failure of docetaxel in patients with castration-resistant prostate cancer. (*Id.* at CabRef0002404).

11. Beardsley discusses Pivot as a reason that a Phase III trial was initiated in mCRPC patients. (JTX-27 at CabRef0002406). However, the authors did not

designate Pivot as being of "special" or "outstanding" interest. (JTX-27 at CabRef0002408; Tr. at 356:23-359:15).

12. A POSA would not expect a drug to be effective against prostate cancer purely based on its effectiveness against breast cancer. (Tr. at 394:5-13).

13. By October 2009, it was known that the Phase III TROPIC study was evaluating whether 25 mg/m^2 of cabazitaxel in combination with daily prednisone would increase overall survival as compared to mitoxantrone with daily prednisone in men with mCRPC and disease progression despite docetaxel. (JTX-27 at 163; JTX-57 at 3784; JTX-66 at 3984; JTX-67; JTX-68).

14. A POSA would know that many clinical trials fail, even at Stage III, including many studies in men with mCRPC. (Tr. at 402:20-404:6).

15. Late stage prostate cancer is heterogeneous, with a wide range in progression rates and drug responses. (Tr. at 386:20-23).

16. A POSA would be at most cautiously optimistic about the prospects of cabazitaxel's success based on Mita, Attard, Pivot, and Beardsley. The existence of the TROPIC trial would have bolstered a POSA's cautious optimism, but would not have provided enough concrete information to take a POSA beyond cautious optimism.

17. The use of H_2 antagonists as premedication for taxanes was known in the art. (Tr. at 306:18-23). The use of H_1 antagonists with cabazitaxel was known in the art. (Tr. at 306:6-9).

18. There were a finite number of premedications typically used with taxanes: H_1 antagonists, H_2 antagonists, and corticosteroids. (Tr. at 262:20-263:11).

19. A POSA would have been motivated to combine cabazitaxel with premedications other than H_1 antagonists based on hypersensitivity reactions that had occurred despite the use of an H_1 antagonist. (Tr. at 306:10-13).

20. A POSA would have arrived at the combination of cabazitaxel and an H2 antagonist through routine experimentation with the small number of available options.

2. Conclusions of Law

The parties agree that there are two differences between the asserted claims of the '777 patent and the prior art. First, while the compound cabazitaxel was known prior to 2009, the prior art did not disclose the administration of cabazitaxel for increasing survival in mCRPC patients. (D.I. 351 at 1, 4, D.I. 360 at 1, 23). Second, although both H_2 antagonists and the use of

premedication with cabazitaxel were known, the use of an H_2 antagonist as a premedication for cabazitaxel was not disclosed. (D.I. 351 at 1, D.I. 360 at 1).

Defendant argues administering cabazitaxel, including at a dose of 20 mg/m^2, to increase survival in mCRPC patients would have been an obvious modification of the prior art studying the compound. (D.I. 351 at 1). Plaintiffs respond that a POSA might have had a motivation to modify the prior art, but certainly would not have had a reasonable expectation of success in doing so, and the modification therefore would not have been obvious. (D.I. 360 at 1). Moreover, Plaintiffs contend that a POSA would especially lack a reasonable expectation of success for the 20 mg/m^2 dose required by claims 2 and 5 of the '777 patent. (*Id.*). For the reasons stated below, I do not find that Defendant has shown by clear and convincing evidence that administering cabazitaxel to increase survival in mCRPC patients—at any dose—would have been obvious to a POSA in 2009. Because of this, I do not address the 20 mg/m^2 dose separately. I likewise do not reach the legal question of whether administering cabazitaxel with an H_2 antagonist would have been obvious to POSA in 2009.

Aside from a brief allusion in opening statements (Tr. at 59:13-17), the parties did not present any argument about secondary considerations of non-obviousness.

a. Motivation to Modify the Prior Art

"For a patent to be obvious, 'some kind of motivation must be shown . . . so that the jury can understand why a person of ordinary skill would have thought of either combining two or more references or modifying one to achieve the patented method.'" *Shire*, 802 F.3d at 1306 (quoting *Innogenetics, N.V. v. Abbott Lab'ys.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008)). The parties disagree about whether a POSA would have been motivated in 2009 to modify the prior art on cabazitaxel by administering it to an mCRPC patient with the intentional purpose of increasing

survival. Defendant argues that the combination of the teachings of Mita, Attard, Pivot, and Beardsley, and the limited public information about the TROPIC trial, would provide a motivation for a POSA to use cabazitaxel to increase a patient's survival. (D.I. 351 at 10-11).

Defendant argues that Mita and Pivot, as clinical studies with positive results, are particularly significant. (*Id.* at 5-6). Defendant asserts that "Mita provide[d] a blueprint for success." (*Id.* at 11). Defendant argues that Mita's promising results would motivate a POSA to try to replicate them. (*Id.* at 11). Defendant notes that *In re Copaxone Consol. Cases* held that previous promising results may provide a motivation to combine. 906 F.3d 1013, 1026 (Fed. Cir. 2018). Defendant further argues that Pivot reinforces Mita's results because it shows that cabazitaxel improved progression-free survival in another docetaxel-resistant cancer. Defendant's expert, Dr. Mark Ratain, testified that even though Pivot was conducted in breast cancer patients, it was still relevant to prostate cancer because the study was conducted in patients with taxane resistance, including docetaxel resistance. (Tr. at 286:16-287:9). Since mCRPC patients faced the same drug resistances, the study would still be informative. (*Id.*). Dr. Ratain also testified that Pivot and Mita together "support[ed] the initiation of Phase III clinical trials of cabazitaxel and taxane-resistant cancers." (*Id.* at 290:12-13).

Defendant presents Attard and Beardsley, contemporaneous review articles, as evidence of how a POSA would have understood Mita and Pivot, respectively. Defendant argues that Attard "also interprets the results reported in Mita to mean that cabazitaxel is active in taxane-resistant (or refractory) CRPC tumors." (D.I. 351 at 8). Defendant asserts that Beardsley's discussion of Pivot is evidence of Pivot's relevance to mCRPC even though Pivot studied a different cancer. (*Id.* at 11).

Defendant further argues that Sanofi's disclosures about the TROPIC trial would also have motivated a POSA to try cabazitaxel. Specifically, because Sanofi was "investing in and conducting a large scale Phase III clinical trial," a POSA would have been motivated to likewise try using cabazitaxel to increase mCRPC patients' survival. (*Id.* at 12).

Defendant finally points to Sanofi's non-public, contemporary statements as evidence of the level of skill in the art, in a similar vein as Attard and Beardsley. (*Id.* at 12). Specifically, in its submission to the FDA regarding the Phase III trial, Plaintiffs said that cabazitaxel was "well suited for development . . . in patients with hormone refractory prostate cancer that progress after Taxotere [docetaxel] based treatment." (DTX-2056.74). Defendant argues that this indicates that a POSA would have had a similar view that cabazitaxel was "well suited," and that the POSA would therefore have been motivated to use it to increase the survival of mCRPC patients. (*Id.* at 12). Similarly, Sanofi scientist Dr. Patricia Vrignaud in deposition testimony stated that cabazitaxel's Phase I results served as "encouragement to pursue" the development of cabazitaxel. (Tr. at 196:13-15).

Plaintiffs challenge the existence of a motivation to combine only with respect to docetaxel-sensitive patients.[6] Plaintiffs argue that a POSA would continue to treat a docetaxel-sensitive patient with docetaxel rather than switch to a new drug. (D.I. 360 at 19). Dr. Nelson testified that he would prefer a "drug that's already shown benefit" to "something experimental." (Tr. at 384:7-11).

Plaintiffs do not argue that a POSA would not be motivated to administer cabazitaxel to docetaxel-refractory patients. Instead, as discussed below, they argue that a POSA would not

[6] Plaintiffs also mention that there is no motivation to try cabazitaxel for patients unable to tolerate docetaxel because of its side effects. (D.I. 360 at 18). As far as I can tell, however, Defendant never argues that cabazitaxel administration to such patients would be obvious.

have a reasonable expectation of success in administering cabazitaxel to docetaxel-refractory patients. (D.I. 360 at 1).

I agree with Defendant that a POSA would have been motivated in 2009 to administer cabazitaxel to mCRPC patients with the purpose of increasing survival. With promising preclinical and Phase I results in mCRPC and Phase II results in another cancer, administering cabazitaxel to increase the survival of mCRPC patients seems at least "obvious to try." *See KSR*, 550 U.S. at 421.

Further, I think this motivation would apply equally to docetaxel-sensitive and docetaxel-refractory patients. The motivation to modify the prior art is not measured relative to the appeal of other options. "[C]ase law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (quoting *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992)). While continuing treatment with docetaxel might be the most desired path for a docetaxel-sensitive patient, I find that a POSA in 2009 would still find cabazitaxel worth trying when considered independently. Thus, a POSA might be more motivated to administer cabazitaxel to docetaxel-refractory patients due to their lack of other treatment options but would still be motivated to administer it to docetaxel-sensitive patients.

b. Reasonable Expectation of Success

For an invention to be found obvious, a POSA must have, in addition to a motivation to modify the prior art, a "reasonable expectation of success" in "achiev[ing] the claimed invention." *Kinetic Concept*, 688 F.3d at 1360. Defendant argues that the same set of prior art references that would have motivated a POSA to modify the prior art also support a reasonable

expectation of success at increasing survival with cabazitaxel. (D.I. 351 at 14). Defendant emphasizes that it is important that the prior art be considered cumulatively, acknowledging that each piece of the prior art on its own might not be sufficient. (D.I. 361 at 1). Defendant argues that the prior art references combined, however, are sufficient, because "conclusive proof of efficacy" is not required. (D.I. 351 at 13-14 (quoting *Acorda Therapeutics v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1333 (Fed Cir. 2018))).

Defendant acknowledges that a POSA might not have had a reasonable expectation of success for all patients. Dr. Ratain testified that "a POSA would expect that some patients would demonstrate increased survival with a 20 to 25 mg dose." (Tr. at 324:1-13). Defendant argues that Mita supports a POSA's reasonable expectation that "at least some patients administered a 20-25 mg/m^2 dose of cabazitaxel would also have increased survival." (D.I. 351 at 14). Dr. Ratain testified, "A POSA would be highly confident just looking at this data alone that there would be many other patients that you could replicate this. In other words, that this is not a one-off." (Tr. at 282:9-12). Defendant acknowledges that two patients is a small sample but argues that Pivot "reinforce[s] a POSA's reasonable expectation of success and demonstrate[s] that the results in Mita are not a fluke." (D.I. 351 at 15). Dr. Ratain testified that Pivot "provides further expectation of success demonstrating in a larger group of patients that cabazitaxel is active in a taxane-refractory cancer." (Tr. at 323:1-10). Defendant again emphasizes that Attard and Beardsley confirm the significance of Mita's and Pivot's results. Beardsley in particular "makes clear that the rationale for Sanofi's initiation of its Phase 3 trial . . . was the success of cabazitaxel in treating taxane-resistant breast cancer." (D.I. 351 at 15).[7]

[7] Defendant also refers to the policy of the American Society of Clinical Oncology (ASCO) and a survey of oncologists. (D.I. 351 at 14 n. 4). Plaintiffs object that using these documents to support the reasonable expectation of success is improper given the lack of substantive testimony

Defendant further argues that the fact that Sanofi, "a large pharmaceutical company," had initiated a Phase III trial would support a POSA's expectation of success. (*Id.* at 16). Dr. Ratain testified, in response to my question, that trials by large pharmaceutical companies were "generally successful." (Tr. at 260:11-261:8). In addition, because it was disclosed that the control arm of the TROPIC trial was mitoxantrone, a drug that increased survival compared to no treatment, Defendant argues that a POSA reading the disclosure would expect cabazitaxel to be "no worse than mitoxantrone." (D.I. 351 at 16). Defendant also argues that Phase III trials may fail for reasons other than efficacy. (*Id.* at 18). Unlike in *Sanofi v. Watson*, a case which did not find a reasonable expectation of success despite the existence of a Phase III trial, Defendant notes that here, cabazitaxel did not have any "negative data," such as safety problems. (D.I. 361 at 7 (citing *Sanofi v. Watson*, 875 F.3d 636, 648 (Fed. Cir. 2017))).

Defendant also argues that Plaintiffs' own statements suggest that a POSA would have had a reasonable expectation of success. (D.I. 351 at 15). That is, Plaintiffs told the FDA that Mita and Pivot demonstrated cabazitaxel's "promising activity," indicating that they themselves had a reasonable expectation of success. (*Id.*). Defendant argues that a POSA looking at Mita and Pivot would therefore have concluded that cabazitaxel was promising, just as Plaintiffs did. (*Id.*).

Plaintiffs take a stricter view of reasonable expectation of success. Plaintiffs assert that Mita's sample was small and the responses in Mita were not significant. (D.I. 360 at 3). Dr.

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about them at trial. Plaintiffs argue that the ASCO report was admitted only to qualify Dr. Nelson, and the survey was struck from Dr. Ratain's expert report. (D.I. 357 at 1-2). Regardless, I find both documents unpersuasive and irrelevant to the reasonable expectation of success inquiry. I was of the same opinion when Plaintiffs objected to the ASCO report at trial. (Tr. at 233:6-233:23). The "expectations" discussed in the two publications have no bearing on the legal standard of "a reasonable expectation of success." Unlike the statements of Dr. Nelson and Dr. Ratain, who explicitly explained that they were applying the legal standard, these statements occurred in a completely separate context. Thus, I disregard the references to these documents.

Nelson testified that "based on a single patient, a POSA would not have an expectation of a response." (Tr. at 386:14-20). Plaintiffs also note that Attard expressed reservations about Mita, questioning whether the drug would be tolerable at the doses necessary for anticancer activity. (D.I. 360 at 6-7).

Plaintiffs argue that Pivot would likewise not provide a reasonable expectation of success because it was conducted in a different cancer. Dr. Nelson testified about the differences between breast and prostate cancer patients. (Tr. at 394:5-395:23). He also opined that a POSA "would not be that impressed" with the results of Pivot. (Tr. at 393:24-394:4). Plaintiffs note that Beardsley, although it reported on Pivot, did not designate it to be of "special" or "outstanding" interest to mCRPC researchers. (D.I. 360 at 17; JTX-27 at 165). Thus, while Pivot's results may have been enough to support the initiation of a Phase III study, Plaintiffs argue that they were not enough to support a reasonable expectation of success.

Plaintiffs further argue that the TROPIC disclosures did not include any data on which a POSA could base a reasonable expectation of success. (D.I. 360 at 9). Plaintiffs argue that the TROPIC disclosures represent a "hope" of success, which is not, as a matter of law, the same as a reasonable expectation. (*Id.* at 9-10). Plaintiffs also challenge Defendant's argument that a POSA would expect the treatment arm of a study to necessarily be "no worse" than the control. (*Id.* at 11). Plaintiffs note that courts may consider the unpredictability of drug development in evaluating a reasonable expectation of success, and that considering that unpredictability here leads to the conclusion that a POSA would not reasonably expect success based on the existence of the TROPIC trial. (*Id.* at 11-12).

Plaintiffs finally argue that Defendant's use of their internal documents is improper because "[t]he inventor's own path itself never leads to a conclusion of obviousness." (*Id.* at 19-

20 (citing *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017))). Plaintiffs note, however, that even to the extent the documents speak to what a POSA would do, they address "the appropriateness of continuing to study cabazitaxel, not expectations of success." (D.I. 360 at 20).

Defendant is correct that I must consider the prior art as a whole. However, even doing so I do not see clear and convincing evidence that a POSA would have reasonably expected success. The parties' fundamental disagreement is about how much of an expectation of success the law requires. The law certainly does not require "conclusive proof of efficacy." *Acorda*, 903 F.3d at 1333. At the same time, cautious optimism is not sufficient, *Sanofi*, 875 F.3d at 650, nor is "hope." *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). While I think the prior art clearly provides for hope and even cautious optimism, I do not think, based on the experts' testimony, that it supports the higher bar of a reasonable expectation of success.

In fact, I do not think Defendant has proven by clear and convincing evidence that a POSA could reasonably expect success even for "at least some patients."[8] Dr. Ratain testified that a POSA would be sure that the impact on the 50-year-old patient in Mita "was not a one-off" because of the magnitude of anticancer activity. (Tr. at 281:16-282:16). Dr. Nelson, however, testified that "it would be very difficult based on an anecdotal patient here to make conclusions about what would happen to the next patient." (*Id.* at 386:23-25). On balance, I found Dr.

[8] I note that Defendant repeatedly argues that a POSA would have a reasonable expectation of success for "at least some patients." (*See, e.g.*, D.I. 351 at 14). I do not think "a reasonable expectation of success for at least some patients" is the same as "a reasonable expectation of success in achieving the claimed invention." Oncology is unpredictable. (Tr. at 107:23-108:6). Expecting success for "at least some patients," would seem to allow a reasonable expectation of success based on the prospect of extremely rare events. The parties did not delve deeply into this issue, however.

Nelson's testimony that a POSA would be hopeful but unsure to be more credible and persuasive than Dr. Ratain's testimony that a POSA would expect success.

Indeed, even the authors in Mita said only that their results were "encouraging" and "warrant further evaluations." (JTX-48 at 723). This sounds to me more like hope than expectation—"further evaluations" in particular suggests less than an expectation of success. Adding Pivot to Mita certainly adds to the hope, but I do not think it creates more than hope. I also do find it notable that Beardsley did not consider Pivot to be of "special" or "outstanding" interest for prostate cancer, suggesting that it did not create any concrete expectation that the results would be transferred to mCRPC. In an area where initially promising inventions may fail at a later stage for a wide array of reasons (*see* Tr. at 402:20-404:6), I am persuaded that data from extremely limited samples or from different populations would not give rise to more than cautious optimism.

I also do not think that the mere existence of a Phase III trial, with no information about its results, would have lifted a POSA's hopes over the bar for a reasonable expectation of success. Dr. Ratain's testimony that large companies' Phase III trials "generally succeed" was bare bones. He referenced a study he had conducted but gave few specifics. Dr. Nelson, by contrast, was able to list a variety of cancer drugs that failed at Phase III. Therefore, I do not think a POSA would reasonably extrapolate from the fact that a Phase III trial had begun that a drug could be expected to be successful.

Considering Plaintiffs' own contemporaneous statements requires care. Plaintiffs rightly assert that their own path should not lead to a conclusion of obviousness. The inquiry is not whether the inventors expected success, but whether a POSA would have expected success. Yet here, it is not clear to me that Plaintiffs' statements indicate that even they had a reasonable

expectation of success. A drug candidate may be "promising" or "well suited for development" and still ultimately not work—much less successfully increase survival, as required by the patent. Thus, I agree with Plaintiffs that "the appropriateness of continuing to study cabazitaxel" is distinct from "expectations of success." (D.I. 360 at 20). I also note that it is clear from the fact that Plaintiffs initiated a Phase III clinical trial that they thought the drug worth studying. Pointing to their explicit statements to that effect does not seem to add any additional persuasive weight beyond that of the Phase III trial's existence.

I find that Defendant did not present clear and convincing evidence that administering cabazitaxel to increase survival in mCRPC patients would have been obvious. I conclude that the asserted claims as a whole are not invalid for obviousness. I do not reach the issue of whether a POSA would have found administering an H_2 antagonist obvious.[9]

IV. CONCLUSION

For the foregoing reasons, I find the asserted claims of the '777 patent infringed and not invalid. In addition, Plaintiffs' Motion to Strike (D.I. 357) is DISMISSED as moot. The parties shall submit a final judgment consistent with this memorandum opinion within one week.

[9] I do nevertheless include some factual findings (section III.C.1 ¶¶ 17-20 *supra*) relevant to the issue.