IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH LLC,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	**Case No. 21 C 1338**
	)	
ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA AB,	)	
	)	
Defendants.	)	

MEMORANDUM OPINION AND ORDER

MATTHEW F. KENNELLY, District Judge:

Wyeth LLC has sued AstraZeneca Pharmaceuticals LP and AstraZeneca AB (collectively AstraZeneca) for infringement of two patents: United States Patent Nos. 10,603,314 (the '314 patent) and 10,596,162 (the '162 patent).[1] Wyeth contends that AstraZeneca, through the promotion and sale of its drug Tagrisso (osimertinib), induced infringement of claims 1, 3, and 9 of the '314 patent and claim 1 of the '162 patent. After a five-day trial, a jury found that the patents were not invalid and that AstraZeneca induced infringement of the patents. AstraZeneca has moved for judgment of a matter of law, arguing that no reasonable jury could have found that (1) AstraZeneca induced infringement of the patents-in-suit; (2) the patents were valid; or (3) that Wyeth suffered damages. In the alternative, AstraZeneca has moved for a new trial on invalidity. For the following reasons, the Court grants AstraZeneca's motion for judgment as a matter

[1] The Court granted the defendants' motion to dismiss Wyeth LLC's co-plaintiff, Puma Biotechnology, Inc., for lack of Article III standing. *See Puma Biotech., Inc. v. AstraZeneca Pharms. LP*, No. 21 C 1338, 2024 WL 1157120 (D. Del. Mar. 18, 2024).

of law on the question of invalidity.

Background

The parties to this suit are pharmaceutical companies that commercialize drugs to treat cancer and other illnesses. The patents-in-suit claim a method of treating a form of non-small cell lung cancer (NSCLC). NSCLC is associated with overactivity of the epidermal growth factor receptor (EGFR), an enzyme that is involved in cell division and growth. Drugs that treat this condition are known as EGFR tyrosine kinase inhibitors (TKIs or inhibitors), and these TKIs bind to certain parts of the EGFR to prevent the enzyme from triggering cancerous cell growth.

Two TKIs, gefitinib and erlotinib (referred to collectively as g/e), showed some promise in treating NSCLC. Gefitinib and erlotinib are classified as "reversible" inhibitors; they form non-covalent bonds with EGFR that dissociate over time. There are two principal limitations to g/e treatment. First, only patients with certain EGFR mutations are sensitive to g/e therapy; the parties refer to these mutations as "sensitizing mutations." In other words, to be a candidate for g/e treatment, a patient needs to have EGFR with the requisite sensitizing mutation(s). Second, "[a] significant limitation in using [reversible inhibitors such as g/e] is that recipients thereof may develop a resistance to their therapeutic effects after they initially respond to therapy, or they may not respond to EGFR-TKIs to any measurable degree at all." '314 Patent at 3:19–23.

The patents-in-suit claim a method for treating "g/e resistant NSCLC." The inventors claim that g/e resistance can be overcome by using "irreversible" EGFR inhibitors that covalently bind to a specific amino acid at a specific location of EGFR.

Specifically, the asserted claims of the '314 patent recite:

> 1. A method for treating gefitinib and/or erlotinib resistant non-small cell lung cancer in a patient in need thereof, comprising administering daily to the patient having gefitinib and/or erlotinib resistant non-small cell lung cancer a pharmaceutical composition comprising a unit dosage of an irreversible epidermal growth factor receptor (EGFR) inhibitor that covalently binds to cysteine 773 residue in the ligand-binding pocket of EGFR or cysteine 805 residue in the ligand-binding pocket of erb-B2.
>
> [. . .]
>
> 3. The method of claim 1, wherein the irreversible EGFR inhibitor covalently binds to cysteine 773 residue of EGFR.
>
> [. . .]
>
> 9. The method of claim 1, wherein the route of administration is oral.

'314 Patent at 35:52–36:65.

The claims of the '162 patent are directed at EGFR with a specific mutation, the "T790M mutation," which is associated with g/e resistance. The asserted claim of '162 patent recites:

> 1. A method of treating gefitinib and/or erlotinib resistant non-small cell lung cancer having a T790M mutation in SEQ ID NO: 1 in a patient, comprising administering daily to the patient having gefitinib and/or erlotinib resistant non-small cell lung cancer having a T790M mutation in SEQ ID NO: 1 a pharmaceutical composition comprising a unit dosage of 2-500 mg of an irreversible EGFR inhibitor that covalently binds to cysteine 773 of the catalytic domain within the SEQ ID NO: 1 having a T790M mutation; wherein the irreversible EGFR inhibitor is not CL-387,785.

'162 Patent at 35:48–36:48.

In September 2021, Wyeth sued AstraZeneca, alleging that AstraZeneca's irreversible EGFR inhibitor Tagrisso (osimertinib) infringes both patents-in-suit. After a claim construction hearing, the Court resolved numerous disputes regarding the meaning of the asserted claims. *See Puma Biotech., Inc. v. AstraZeneca Pharms. LP*,

21 C 1338, 2023 WL 2683559 (D. Del. Mar. 29, 2023). AstraZeneca then moved for summary judgment, arguing in relevant part that (1) the patents were invalid because they failed to meet the enablement and written description requirements of 35 U.S.C. § 112; and (2) the use of Tagrisso did not infringe the asserted claims. The Court concluded that there were genuine disputes of material fact regarding invalidity and infringement and therefore denied summary judgment on those points. *See Puma Biotech., Inc. v. AstraZeneca Pharms. LP*, No. 21 C 1338, 2024 WL 1157120 (D. Del. Mar. 18, 2024).

After a five-day trial, a jury concluded that the patents were not invalid and that AstraZeneca induced infringement of the patents. A key dispute at trial was whether, and to what extent, each of Tagrisso's indications (i.e., FDA-approved uses) infringed. Tagrisso currently has three FDA-approved indications listed on its product label. Originally, Tagrisso was FDA-approved only "for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy." JTX-5 (2015 Tagrisso Label).[2] The parties refer to this as the "second-line" or "2L" indication, in reference to the fact that the drug would only be prescribed after some other primary or "first-line" treatment had failed.

Subsequently, Tagrisso was FDA-approved for "the first-line treatment of adult patients with metastatic NSCLC whose tumors have [g/e sensitizing mutations], as indicated by an FDA-approved test." JTX-14 (2023 Tagrisso Label). The parties refer

[2] For simplicity, the Court refers to the parties' exhibits in the same format as the parties: "DTX" indicates the defendants' trial exhibit, "PTX" indicates the plaintiff's trial exhibit, and "JTX" indicates a joint trial exhibit.

to this as the "first-line" or "1L" indication, in reference to the fact that the drug would be prescribed as the primary or first treatment for the patient. Tagrisso was also FDA-approved "as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have [g/e sensitizing mutations], as detected by an FDA-approved test." JTX-14 (2023 Tagrisso Label). The parties refer to this as the "adjuvant" indication, in reference to the fact that the drug would be prescribed as a follow-up to a primary treatment (in this case, surgery to remove a tumor) to target cancer cells that the primary treatment did not eliminate.

Wyeth argued that AstraZeneca induced infringement of the patents-in-suit with respect to all three indications of Tagrisso. Although the first-line and adjuvant indications are not directed at patients who have received and failed on g/e treatment, Wyeth asserted that prescribing doctors nevertheless infringe the patents-in-suit with respect to these "pretreatment" indications because they sometimes intend to proactively treat g/e resistance when prescribing under these indications. The jury concluded that AstraZeneca induced infringement with respect to all three indications and awarded Wyeth $107,500,000 in damages. The Court later held a two-day bench trial on AstraZeneca's equitable defenses and its counterclaim that the patents were invalid due to indefiniteness. The Court found that AstraZeneca did not show by clear and convincing evidence that the patents were unenforceable or that they were invalid for indefiniteness. *See* August 6, 2024 Findings of Fact & Conclusions of L, dkt. no. 515.

Discussion

The Court should grant judgment as a matter of law "only if, viewing the evidence

in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find' for the nonmovant." *TransWeb, LLC v. 3M Innovative Properties Co.*, 812 F.3d 1295, 1301 (Fed. Cir. 2016) (quoting *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)).

A. Infringement

AstraZeneca first argues that it is entitled to judgment as a matter of law on Wyeth's induced infringement claim because the evidence was insufficient to support a finding of direct infringement or induced infringement regarding any of Tagrisso's three indications. Although Wyeth sued AstraZeneca only under a theory of induced infringement, *see* 35 U.S.C. § 271(b), "direct infringement is a necessary predicate for a finding of induced infringement in the usual patent infringement case." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018). In addition to establishing that some direct infringement occurred, the plaintiff must also establish "that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement." *Id.* (quoting *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)). "Circumstantial evidence can support a finding of specific intent to induce infringement." *Id.* (quoting *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010)); *see also DSU Med. Corp.*, 471 F.3d at 1306 ("While proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice."). "Infringement is a question of fact." *Godo Kaisha IP Bridge 1 v. TCL Commc'n Tech. Holdings Ltd.*, 967 F.3d 1380, 1383 (Fed. Cir. 2020).

1. Direct infringement

AstraZeneca argues that Wyeth failed to provide evidence of direct infringement to the jury because it did not show that "prescribers intend to treat g/e resistant NSCLC when prescribing Tagrisso" or that prescribers "actually treat g/e resistant NSCLC, that is, administer Tagrisso to a patient who has g/e resistant NSCLC." Defs.' Post-Trial Mot. at 2 (emphasis omitted). Wyeth asserts that it produced sufficient evidence on both points.

a. Intent

Regarding prescribers' intent to treat g/e resistant NSCLC, the Court concludes that Wyeth produced sufficient evidence for a reasonable jury to conclude that at least some doctors intended to treat g/e resistant NSCLC when prescribing Tagrisso in all three indications. As an initial matter, the Court notes that AstraZeneca does not offer any colorable argument that Wyeth failed to carry its burden on direct infringement with respect to Tagrisso's second-line indication. The Court agrees that the second-line indication "is specifically directed to patients who have already failed on a previous TKI therapy like gefitinib and who have the T790M mutation." Pl.'s Resp. at 2; *see also* JTX-5 (2015 Tagrisso Label); JTX-15 (2023 Tagrisso Label). It was therefore reasonable for the jury to conclude that at least some physicians prescribed Tagrisso for the express purpose stated in the indication, i.e., treating g/e resistant NSCLC.

With respect to the first-line and adjuvant indications, AstraZeneca's central argument is that Wyeth was required to either call prescribing physicians to testify regarding their intent when prescribing Tagrisso or to present survey evidence from physicians on their prescribing intentions. The Federal Circuit, however, has stated that

"[t]o support the verdict, the record does not need to contain direct evidence" of direct infringement because "[i]t is hornbook law that direct evidence of a fact is not necessary." *Metabolite Lab'ys, Inc. v. Lab'y Corp. of Am. Holdings*, 370 F.3d 1354, 1364–65 (Fed. Cir. 2004). "Circumstantial evidence is not only sufficient, but may also be more certain, satisfying and persuasive than direct evidence." *Id.* (quoting *Moleculon Rsch. Corp. v. CBS Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986)). It is therefore sufficient if "the record contains sufficient circumstantial evidence to permit the jury to imply that physicians directly infringe." *Id.*; *see also Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1318 (Fed. Cir. 2009) (concluding that "circumstantial evidence was just adequate to permit a jury to find that at least one . . . person within the United States during the relevant time period . . . had performed the claimed method").

The Court concludes that Wyeth carried its burden. The jury was entitled to credit the testimony of Wyeth's expert, Dr. Glen Weiss, a physician specializing in the treatment of lung cancer, who explained that physicians prescribe Tagrisso in all three indications for the purpose of treating g/e resistance. *See, e.g.*, Jury Trial Tr. at 183:9–21 (Weiss testimony) (explaining that prescribing the second-line indication of Tagrisso infringes that patents-in-suit because "[i]n order for patients to be eligible in this second-line setting, they had to have disease that progressed on or after EGFR tyrosine kinase inhibitor therapy like gefitinib, so that would be gefitinib-resistant non-small cell lung cancer, and they also have a T790M mutation"); *id.* at 188:2–10 ("Well, about 35 percent of these patients that have pretreatment, never been exposed to an EGFR directed therapy, will have a T790M mutation in their tumor. And doctors are well aware that resistance to gefitinib or drugs like gefitinib are a big problem. And in order to

decrease that risk of exposure and having these patients on a brief time frame with those drugs, it's better to give Tagrisso up front to delay or to prevent the T790M resistance from being a problem"); *id.* at 188:24–189:15 (Q: In your experience, are oncologists who treat non-small cell lung cancer generally aware of the problems related to T790M and resistance who are in the pretreatment population? A: Yeah, I believe they're aware of this problem. Q: And does that knowledge play a role with respect to how they treat these patients? A: Yes. Having awareness that T790M mutation is a problem for patients, approximately 35 percent, giving a patient a reversible inhibitor which does not overcome the T790M resistance can be a problem for these patients. They often have a shorter duration of time before they progress and some of them—before they're able to get any other therapy like Tagrisso, and some of these patients may not live long enough if you tried something else first before giving Tagrisso because their cancer may continue to spread or cause them significant problems where they're not eligible for additional treatment."); *id.* at 190:1–2 (explaining that the possibility of a T790M mutation is "a big problem for clinicians in making treatment decisions").

AstraZeneca argues that Dr. Weiss's testimony provides no support for a finding that an act of direct infringement occurred. It argues that "[g]enerally, expert witnesses are not permitted to testify regarding intent, motive, or state of mind, or evidence by which such state of mind may be inferred." Defs.' Post-Trial Mot. at 3. This is not a case, however, where Dr. Weiss was speculating on the specific state of mind of a specific physician. Rather, Dr. Weiss testified regarding general practices, standards of care, and the different variables that underly treatment decisions in his specialty field of

lung cancer treatment. He was well-qualified to testify on these points, and the jury could reasonably infer from his testimony that at least some doctors acted in accordance with these practices. *See, e.g.*, *Packet Intel. LLC v. NetScout Sys., Inc.*, 965 F.3d 1299, 1316 (Fed. Cir. 2020) (jury was permitted to draw a reasonable inference regarding infringement from evidence presented at trial).

AstraZeneca also argues that Dr. Weiss testimony at most goes to treating doctors' "knowledge or awareness" and not whether they acted with an "intentional purpose." Defs.' Post-Trial Mot. at 4. Again, however, the jury was permitted to draw the straightforward inference that when prescribing Tagrisso, doctors would have applied their knowledge regarding what would extend their patient's lifespan.

AstraZeneca next argues that Dr. Weiss testified only that doctors prescribe Tagrisso to "prevent[ ]" or "delay[ ]" g/e resistance, not to "treat" g/e resistance. Defs.' Post-Trial Mot. at 4. In fact, however, Dr. Weiss testified that doctors prescribe Tagrisso to "prevent[ ]" or "delay[ ]" *problems* associated with g/e resistance. Jury Trial Tr. at 188:6–10; *see also id.* at 189:6–15 ("[G]iving a patient a reversible inhibitor which does not overcome T790M resistance can be a problem for these patients . [. . .] [S]ome of these patients may not live long enough if you tried something else first before giving Tagrisso because their cancer may continue to spread or cause them significant problems where they're not eligible for additional treatment."). Viewing the testimony in the light most favorable to Wyeth, as the Court must do when reviewing the jury's verdict in Wyeth's favor, this testimony supports Wyeth's position that prescribing physicians intend to treat g/e resistance (and thus avoid the "problems" that g/e resistance will cause patients to suffer).

Moreover, Dr. Weiss's testimony was not Wyeth's only evidence regarding direct infringement. Wyeth also presented evidence that AstraZeneca designed Tagrisso with the goal of targeting g/e resistance and marketed Tagrisso to physicians as "designed to inhibit EGFR sensitizing and resistance mutations." *See* PTX-447 at 2. This marketing was not limited to Tagrisso's second-line indication. *See id.* ("Don't miss a patient who could be eligible for first-line TAGRISSO."). Again, the jury was entitled to draw the straightforward inference that doctors used Tagrisso in accordance with how the drug was marketed to them. *See Lucent Techs., Inc.*, 580 F.3d at 1318 (holding that the plaintiff produced sufficient circumstantial evidence of direct infringement to support the jury's verdict where "[the defendant] not only designed the accused products to practice the claimed invention, but also instructed its customers to use the accused products in an infringing way").

Finally, AstraZeneca briefly argues that the evidence is insufficient to support the verdict with respect to the adjuvant indication because, it contends, gefitinib and erlotinib are not suitable for adjuvant treatment. AstraZeneca thus argues that doctors "would [not] have any plausible reason to be thinking or concerned about resistance to drugs they would not use." Defs.' Post-Trial Mot. at 4. But AstraZeneca never presented any evidence or argument along these lines to the jury. In fact, AstraZeneca's closing arguments suggested the opposite of what it now argues. *See* Jury Trial Tr. at 1105:9–15 (stating that, with respect to "adjuvant and first-line . . . Tagrisso is being used here where gefitinib would have otherwise been used because Tagrisso is better"); Jury Trial Tr. at 1126:21–25 ("Second, first-line adjuvant, those are sensitive patients. . . . Those are patients who would have received gefitinib,

but AstraZeneca developed something better."). The Court cannot grant judgment as a matter of law to AstraZeneca based on facts or evidence that it did not present at trial. Moreover, to the extent that AstraZeneca argues that it was Wyeth's burden to show that gefitinib and/or erlotinib are regularly used in the adjuvant context, the Court disagrees. Although Wyeth had to prove infringement by preponderance of the evidence, that does not mean it was required to anticipate and rebut every possible counterpoint that AstraZeneca might have raised. As discussed, Wyeth presented sufficient evidence that at least some physicians intend to treat g/e resistance in the adjuvant context.

b. Treatment of patients having g/e resistant NSCLC

AstraZeneca argues that Wyeth "presented no evidence of patients treated according to Tagrisso's 1L or Adjuvant indications who would not respond if given g/e" and therefore did not establish that patients "having g/e resistant" NSCLC were treated, as required by the asserted claims. Defs.' Post-Trial Mot. at 5. But Wyeth presented ample evidence that the T790M mutation confers resistance to g/e and that this mutation is present in some patients even before treatment with g/e. *See, e.g.*, '314 Patent at 4:37–38 ("The T790M mutation confers resistance to gefitinib and/or erlotinib treatment."); Jury Trial Tr. at 166:18–23 (Weiss testimony) ("So it's been reported by many that the T790M mutation is a resistance mutation, it can explain resistance to gefitinib."); Jury Trial Tr. at 224:23–225:6 (Berger testimony) ("Q: What did you determine the prevalence of T790M to be in this pretreatment population [of first-line and adjuvant patients]? A: So I found the prevalence to be at least 35 percent."). The Court therefore sees no basis to find that the jury could not credit this evidence and

conclude that at least some patients receiving Tagrisso in the first-line and adjuvant indications had g/e resistant NSCLC.

2. Induced infringement

AstraZeneca also argues that Wyeth failed to present sufficient evidence that AstraZeneca induced infringement with respect to all three indications of Tagrisso. With respect to the second-line indication, AstraZeneca argues that it "deliberately stopped promoting Tagrisso's 2L use in 2018—before the patents issued." But the second-line indication has remained on Tagrisso's label, and Wyeth presented evidence that second-line prescriptions continued to generate sales for AstraZeneca after the patents issued. *See* Jury Trial Tr. at 350:17–20 (Rao testimony). The jury was permitted to conclude from these facts that AstraZeneca "possessed specific intent to encourage another's infringement." *Vanda Pharms. Inc.*, 887 F.3d at 1129.

With respect to the first-line and adjuvant indications, Wyeth presented evidence that AstraZeneca consistently emphasized Tagrisso's ability to combat the T790M resistance mutation as a key feature of its new drug and that this marketing strategy was not limited to the second-line indication (which AstraZeneca itself alleges it stopped promoting in 2018). *See, e.g.*, PTX-448 (TAGRISSO is a third-generation, irreversible EGFR TKI designed to . . . inhibit mutated EGFR with the T790M resistance mutation."); PTX-114 ("TAGRISSO is a *better EGFR-TKI* that addresses significant areas of unmet need in EGFRm NSCLC" including "overcome[ing] T790M resistance"); PTX-114 (stating that AstraZeneca's 2018–2021 "strategy" included "advocacy for 1L TAGRISSO use (vs. waiting until 2L)"). This is sufficient to support the jury's determination that AstraZeneca induced infringement with respect to Tagrisso's first-line and adjuvant

indications. *See Lucent Techs., Inc.*, 580 F.3d at 1322 (stating that "advertising an infringing use[ ] can support a finding of an intention for the product to be used in an infringing manner"). Although AstraZeneca presented contrary evidence regarding its intent to promote treatment of g/e resistant NSCLC with respect to the pretreatment indications, the jury was not required to credit this evidence.

In sum, the Court concludes that AstraZeneca is not entitled to judgment as a matter of law on infringement.

B. Invalidity

AstraZeneca argues that it is entitled to judgment as a matter of law on its counterclaim that the patents-in-suit are invalid due to anticipation, obviousness, lack of enablement, and lack of written description.

1. Anticipation

AstraZeneca argues that the asserted claims of the '314 patent are invalid due to anticipation. "Under 35 U.S.C. § 102, a prior art reference will anticipate a patent claim if it discloses all of the limitations of the claim 'arranged or combined in the same way as in the claim.'" *Incept LLC v. Palette Life Scis., Inc.*, 77 F.4th 1366, 1371 (Fed. Cir. 2023) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–70 (Fed. Cir. 2008)). Anticipation can be express or inherent. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). "Anticipation is a question of fact." *Incept LLC*, 77 F.4th at 1371.

AstraZeneca cites to a 2003 article entitled "CI-1033, an Irreversible pan erbB Receptor Inhibitor and its Potential Application for the Treatment of Breast Cancer," which the parties refer to as "Allen 2003" in reference to its first author. *See* DTX-73.

The article states that the compound CI-1033, which it describes as "an irreversible, pan-erbB inhibitor, has the potential to have an important role in the future treatment of breast and other cancers." *Id.* at 2. Although the article focuses on breast cancer, it also mentions NSCLC. *See, e.g., id.* at 4. The article discusses orally administering a daily dosage of 50 to 650 milligrams of CI-1033 per day. AstraZeneca therefore argues that Allen 2003 "disclosed each and every element of the Asserted Claims of the '314 patent." Defs.' Post-Trial Mot. at 25.

The Court disagrees that AstraZeneca has shown by clear and convincing evidence that Allen 2003 anticipates the asserted claims of the '314 patent such that no reasonable jury could conclude otherwise. Allen 2003 is focused primarily on breast cancer, not NSCLC. Although Allen 2003 briefly discusses NSCLC, it is undisputed that it does not mention or discuss g/e resistance, which is a key component of the claimed invention. AstraZeneca relies on the fact that Allen 2003 mentions NSCLC with "EGFRvIII," which AstraZeneca asserts a POSA would have known is a g/e resistant variant of NSCLC. As evidence of a POSA's knowledge, AstraZeneca points to a 2004 article entitled "Resistance to Tyrosine Kinase Inhibition by Mutant Epidermal Growth Factor Receptor Variant III Contributes to the Neoplastic Phenotype of Glioblastoma Multiforme," which the parties refer to as "Learn 2004" in reference to its first author. *See* DTX-116. Because anticipation is limited to a single reference, AstraZeneca cannot argue that the combined teachings of Allen 2003 and Learn 2004 render the patent invalid as anticipated.[3] *See Arbutus Biopharma Corp.*, 65 F.4th at 662.

[3] AstraZeneca does not raise a defense of obviousness based on the combination of Allen 2003 and Learn 2004.

AstraZeneca instead asserts that Learn 2004 is evidence of what a POSA would know with respect to EGFRvIII when reading Allen 2003.

Even so, Allen 2003 does not cite or discuss any studies involving the treatment of EGFRvIII with CI-1033. In addition, Wyeth's expert, Dr. Frederick Hausheer, testified that Allen 2003 speculates that EGFRvIII would respond to any EGFR inhibitor (which would include g/e). *See* Jury Trial Tr. at 919:8–15 ("Allen has a mention of this EGFR variant III here, and you can see what he says at the very end. He says small molecule RTK inhibitors. He's saying that—he's not making any distinction with respect to reversible or irreversible. He says anything should work, and there's absolutely no experimental evidence in this article. This is pure speculation. There's no evidence."). Finally, Allen 2003 focuses only on a specific compound, CI-1033. Although it highlights the fact that it is an irreversible EGFR inhibitor, it does not draw the conclusion that *any* irreversible EGFR inhibitors that covalently binds to cysteine 773 will be effective at treating g/e resistant NSCLC. The jury therefore was not required to find that Allen 2003 disclosed all elements of the claim "arranged or combined in the same way as in the claim[s]" of the '314 patent or that the '314 patent was "the natural result flowing from the operation as taught in the prior art." *Incept LLC*, 77 F.4th at 1371 (quoting *Net MoneyIN, Inc.*, 545 F.3d at 1369–70 (Fed. Cir. 2008)); *Arbutus Biopharma Cor.*, 65 F.3d at 662.

2. Obviousness

AstraZeneca next argues that the asserted claims of the '314 patent and the '162 patent are invalid for obviousness. "Obviousness is a question of law based on underlying factual determinations." *Incept LLC*, 77 F.4th at 1371. "Those underlying

factual determinations include: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations such as commercial success, long felt but unsolved needs, and failure of others." *Id.* In contrast to the defense of anticipation, the defense of obviousness can be based on a combination of prior art references. But "[a] determination of obviousness 'requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.'" *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1365 (Fed. Cir. 2022) (quoting *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019)). The jury may also consider whether the reference "teach[es] away from a claimed combination," which weighs against a finding of obviousness. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017).

a. '314 Patent

AstraZeneca asserts that the asserted claims of the '314 patent are obvious considering the combination of Allen 2003 and an additional prior art reference that the parties call "Agus 2003." Agus 2003 is a patent application entitled "Method of Treating Cancer Using Kinase Inhibitors." *See* DTX-71. Although Agus 2003 discusses the problem of g/e resistance in a broad sense, the jury was not required to find that a POSA would be motivated to combine Allen 2003 and Agus 2003 such that the asserted claims would be obvious. As Dr. Hausheer testified, the '314 patent teaches a completely different approach to treating g/e resistant NSCLC than Agus 2003. The method of treatment in the '314 patent involves a daily dosage of an irreversible EGFR

inhibitor that covalently binds to cysteine 773. In other words, the inventors' central discovery is that irreversible EGFR inhibitors can get the job done where reversible inhibitors like g/e cannot. Agus's approach, in contrast, is to *overdose* patients with increasing amounts of *any* inhibitor without regard to whether it is reversible or irreversible. *See, e.g.*, DTX-71 at 3:10–12 ("The method includes administering to patients a resistance surmounting quantity of a TKI which may be administered with less frequency than conventional TKI treatments."). In fact, Agus 2003 teaches, for example, administering an increased weekly dosage of *gefitinib*, whereas the patents-in-suit are directed at using a different class of compound (irreversible EGFR inhibitors) to treat g/e resistant NSCLC. *See, e.g.*, *id.* at 6:7–10 ("The inventor also surprisingly demonstrated that weekly IRESSA [gefitinib] dosages at an amount significantly greater than the recommended daily dosing was well tolerated and can inhibit tumor growth effectively . . . even in tumors that demonstrated a resistance to conventional TKI therapy.").

Even setting aside the fact that Agus 2003 teaches away from the claimed invention, the jury was not required to find that Agus 2003 makes up for all of the shortcomings the Court discussed with respect to Allen 2003. For example, Wyeth's expert, Dr. Hausheer, testified that Agus 2003 does not distinguish between mutated and non-mutated forms of NSCLC. *See* Jury Trial Tr. at 923:14–18 ("Agus is teaching to overdose once or twice a week as a treatment for non-mutated—he's not—there's no resistance; there's no T790M. You just treat any type of tumor, and he's got prostate cancer as his main example."). In addition, neither Allen 2003 nor Agus 2003 posit that g/e resistant NSCLC can be treated using the entire class of irreversible EGFR

inhibitors that covalently bind to cysteine 773. For these reasons, the jury was not required to find that the asserted claims were obvious in light of the combination of Allen 2003 and Agus 2003.

b. '162 Patent

AstraZeneca also argues that the '162 patent was obvious considering the combination of Allen 2003 and Kobayashi 2005. As a preliminary matter, the parties vigorously dispute whether Kobayashi 2005 is prior art. Specifically, the parties dispute whether the inventors of the '162 patent conceived of their invention before or after Kobayashi was published in February 2005. The Court need not resolve this dispute, however, because it concludes that even if Kobayashi 2005 is considered prior art, there was sufficient evidence for the jury to conclude that the combination of Allen 2003 and Kobayashi 2005 did not render the asserted claim of the '162 Patent obvious. In particular, Dr. Hausheer testified that a POSA would not have a motive to combine Allen 2003 and Kobayashi 2005, given that the references discuss different diseases and different mutations. *See, e.g.*, Jury Trial Tr. at 925:16–23. AstraZeneca did not provide clear and convincing evidence to the contrary that would leave a reasonable jury no choice but to credit AstraZeneca's expert witness over Wyeth's expert witness. In fact, AstraZeneca introduced hardly any evidence on this point beyond its expert's unelaborated testimony. *See* Jury Trial Tr. at 581:25–582:9 (Reider testimony) ("I have been instructed that in obviousness you can combine two or more references if a person of skill in the art would be motivated to look at them. And in this case, the Kobayashi paper, which came out in 2005, combined with a reference called Allen, which is from 2003, two years earlier, disclose all the elements of the asserted claims.

So if you look at—a POSA would have reason to combine them, and if you take the information in those two prior art references, they have everything that's in these patents with regard to the claimed invention."); *id.* at 585:17–22 ("Q: And would a POSA in 2005 be motivated to follow Kobayashi's description of the effectiveness of an irreversible EGFR inhibitor on T790M mutant-resistant non-small cell lung cancer by using the irreversible inhibitor described in Allen? A: Yes."). Indeed, Kobayashi 2005 does not cite to Allen 2003, which supports Wyeth's argument that a POSA would not have been motivated to combine the two because they addressed different diseases and mutations. The Court therefore cannot say that AstraZeneca presented clear and convincing evidence that the '162 patent was invalid due to obviousness.

3. Enablement

The Court next addresses AstraZeneca's argument that the patents-in-suit are invalid because they are not enabled. A patent must include a specification which contains "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention." 35 U.S.C. § 112(a). The Federal Circuit has interpreted section 112(a) as containing both a "written description" requirement and an "enablement" requirement. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010).

"Enablement is a legal question based on underlying factual determinations." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 684 (Fed. Cir. 2015).

"Because patents are presumed valid, lack of enablement must be proven by clear and convincing evidence." *Baxalta Inc. v. Genentech, Inc*., 81 F.4th 1362, 1365 (Fed. Cir. 2023). The enablement requirement is satisfied if the specification contains sufficient information to permit "a person of skill in the art to make and use the claimed invention." *Vasudevan Software, Inc.*, 782 F.3d at 684. "[T]he specification must enable the full scope of the invention as defined by its claims." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). Thus, "[i]f a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class." *Id.* This does not mean, however, that "a specification necessarily [is] inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing." *Id.* at 611. "[A] specification may call for a reasonable amount of experimentation to make and use a patented invention." *Id*. at 612. "In other words, 'the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'"[4] *Baxalta Inc.*, 81 F.4th at 1365 (quoting *MagSil Corp. v. Hitachi Glob. Storage Techs.*, Inc., 687 F.3d 1377, 1380 (Fed. Cir. 2012)). Factors that may be considered to determine whether a claimed invention requires undue experimentation include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

[4] After the Supreme Court's decision in *Amgen*, the Federal Circuit has used the terms "undue experimentation" and "unreasonable experimentation" interchangeably. *See Baxalta Inc.*, 81 F.4th at 1365–66, 1367 n. 4.

Amgen Inc., 987 F.3d at 1084 (quoting *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)); *see also Baxalta Inc.*, 81 F.4th at 1367 ("We do not interpret [the Supreme Court's decision in] *Amgen* to have disturbed our prior enablement case law, including *Wands* and its factors.").

AstraZeneca challenges three aspects of the asserted claims as not enabled. First, it argues that the patents-in-suit claim but do not enable the use of "***any*** compound that functions to covalently bind to cysteine 773 and irreversibly inhibit EGFR." Defs.' Post-Trial Mot. at 9–10. Second, it argues that the patents claim but do not enable treatment of "the full sweep of g/e resistant NSCLC." *Id.* Third, it argues that the patents claim but do not enable treatment via a "unit dosage—i.e., a predetermined quantity of active material calculated to produce the desired therapeutic effect." *Id.* (internal quotation marks omitted) (emphasis omitted).

a. Any compound

AstraZeneca first argues that the patents-in-suit do not enable a POSA to practice the claimed method of treatment with the full scope of compounds that covalently bind to cysteine 773 and irreversibly inhibit EGFR. According to AstraZeneca, the asserted claims cover "hundreds of billions" of chemical compounds and "leave it to a POSA to undertake the extraordinarily onerous and unpredictable task" of determining which compounds in fact treat g/e resistant NSCLC. Defs.' Post-Trial Mot. at 11 (emphasis omitted).

The Court addressed AstraZeneca's arguments in detail at the summary judgment stage and concluded that "there [was] a genuine factual dispute regarding whether the specification would enable a POSA to practice the claims with *all*

'compound[s] that irreversibly inhibit[ ] EGFR and covalently bind[ ] to [cysteine 773 residue in the ligand-binding pocket of EGFR or cysteine 805 residue in the ligand-binding pocket of erb-B2 / cysteine 773 of the catalytic domain within the SEQ ID NO: 1 having a T790M mutation]' without undue experimentation." *Puma Biotech.*, 2024 WL 1157120, at *7. The evidence presented to the jury at trial was very similar to the evidence submitted to the Court at summary judgment, and AstraZeneca provides no reason for the Court to reconsider at this stage its conclusion that this was appropriately left to the jury's determination.

First, although AstraZeneca argues that a POSA would be required to unduly experiment with billions of compounds to determine whether they treat g/e resistant NSCLC, Wyeth's expert, Dr. Jorgensen, testified that the universe of possible compounds was not in the billions, but rather far smaller. *See* Jury Trial Tr. at 962:9. Dr. Jorgensen further testified that a POSA would understand that the universe of possible compounds would be limited by certain features that would be required for the compound to covalently bind to cysteine 773. *See, e.g.*, Jury Trial Tr. at 977:5–21 ("Q: [AstraZeneca's expert] Dr. Reider suggested that basically any kind of core could be used to make an inhibitor that would be able to covalently bind to cysteine 773. Do you agree with that? A: Well, one can envision a world of cores, and from looking at that structure that I illustrated before of the slot in the protein and having to have a slot-like molecule, you're going to have to have cores that let the molecule be quite flat. So that's going to limit the cores. Also, there are other limitations. You have to have a nitrogen atom in the core that's capable of hydrogen bonding to that methionine hinge region to pin -- help pin the inhibitors, and we see that in these EGFR inhibitors. Plus you're

going to have to have -- the core has to have 19 substituents placed so that you can have the covalent bond form to cys 773. So there are a lot of restrictions on the size."). In addition, Dr. Jorgensen critiqued AstraZeneca's evidence, stating that it amounted to an "exaggeration" of the number of possible compound structures based on trivial substitutions. *See* Jury Trial Tr. at 979:11–25 ("I find [AstraZeneca's expert's slide] and a lot of the AstraZeneca presentation to involve exaggeration and also sort of attempts to confuse. I can just point out some things here. So I'll point immediately to the warhead in their highlighting in purple, what he's now calling dimethylaminobutenamide warhead. If you show that to any medicinal chemist and say what's the warhead, they're going to say it's an acrylamide. It just has a substituent on it that's a minor variation. It's like adding an extra mirror on your automobile. So that's just trying to say, oh, different warhead."); *see id.* at 980:20–24 ("And medicinal chemists would look at these structures and see the similarities, the core, the heteroaryl group or the aryl and the acrylamide, and there's no big difference here at all. Same intellectual entities."); *see id.* at 993:22–994:3 ("You're misrepresenting a POSA. A POSA is focused. He or she, making kinase inhibitors, focuses on a core of crystal structures that very much restricts the substituents that you can put on the core. It's not an isolated molecule that you can infinitely substitute as you take one of these structures from a composition-of-matter patent.").

Second, the parties' experts disagreed regarding the amount of guidance provided by the specification with respect to the required structure for irreversible EGFR inhibitors and the representativeness of the three examples provided in the specification. As the Court discussed at the summary judgment stage, the key question

is not whether the specification "describe[s] with particularity how to make and use every single embodiment within a claimed class," but rather "whether the specification describes some 'general quality' or 'rule' that 'may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset' without having to engage in an '[un]reasonable amount of experimentation.'" *Puma Biotech., Inc*, 2024 WL 1157120, at *7 (quoting *Amgen Inc.*, 598 U.S. at 611–12). Dr. Jorgensen testified that the examples, information in the specification, the references disclosed in the patent, and the knowledge and experience of a POSA would be sufficient to enable a POSA to practice the claimed method-of-treatment. *See* Jury Trial Tr. at 962:17–981:7. The jury was not required to credit AstraZeneca's expert over Wyeth's with respect to these issues.

Third, AstraZeneca cites to the fact that the specification states that the chosen irreversible EGFR inhibitor "may also be a larger compound," which the parties agree is, in fact, not suitable for carrying out the claimed method-of-treatment. Defs.' Post-Trial Mot. at 15. But as the Court discussed in its decision on AstraZeneca's motion for summary judgment, the mention of "larger compound[s]" in the specification does not necessarily invalidate the patents:

> Although it is true that an inventor must enable the full scope of the claim, here, the asserted claims covers only those irreversible EGFR inhibitors that 'covalently bind[ ]' to the specified part of EGFR. The relevant question, therefore, is whether the patent enables a POSA to identify which irreversible EGFR inhibitors will covalently bind to the specified part of EGFR without "undue experimentation." *Baxalta Inc.*, 81 F.4th 1362 at 1365.

Puma Biotech., 2024 WL 1157120, at *6.

Wyeth presented evidence, which the jury was entitled to credit, that a POSA

would not be misled by this statement because a POSA would know that large compounds cannot covalently bind to cysteine 773 of EGFR. *See* Jury Trial Tr. at 977:21–24 (Jorgensen testimony) ("So there are a lot of restrictions on the size. You couldn't have a super large core. That wouldn't fit. It might also not be flexible enough to adjust to the lock. So there are a lot of limitations on reasonable cores. [. . .] A POSA in 2005 is focusing on small molecules [. . .] That was what dominated the literature, and it's consistent with having to get inside the cell.").

In sum, Dr. Jorgensen's conclusion was that identifying irreversible EGFR inhibitors that covalently bind to cysteine 773 would be "a slam dunk, no problem," for a POSA in 2005. Jury Trial Tr. at 983:4; *see also id.* at 982:23–983:1 (stating that "testing for them being irreversible inhibitors is straightforward, and this is in 2005. There are all sorts of things you can do easily in a day. [. . .] And a competent POSA would be able easily to design irreversible inhibitors of EGFR just as I did for two other proteins."). Thus, as the Court concluded at the summary judgment stage, the question of whether the patents-in-suit enabled a POSA to practice the claims with the full scope of the specified class of compounds turned on multiple factual disputes. The jury was entitled to conclude that AstraZeneca did not show by clear and convincing evidence that the patents were not enabled on this basis.

b. g/e resistance

AstraZeneca next argues that the patents do not meet the enablement requirement because the patents-in-suit "fail[ ] to teach how to treat broad categories of g/e resistant NSCLC." Defs.' Post-Trial Mot. at 20. Specifically, AstraZeneca argues that the method of treatment taught by the patents is not effective for patients with

NSCLC that lacks sensitizing mutations, NSCLC with MET amplification, or NSCLC with a KRAS mutation. AstraZeneca raised the same argument at the summary judgment stage. Again, the Court declined to grant summary judgment on this basis because it concluded that there was a genuine dispute regarding whether a POSA would consider these types of NSCLC to be g/e resistant. *See Puma Biotech., Inc.*, 2024 WL 1157120, at *7. AstraZeneca provides no reason for the Court to revisit its conclusion on this issue now.

Wyeth presented ample evidence to the jury that a POSA would not understand the disputed categories of NSCLC to be "g/e resistant." For example, Wyeth's experts persuasively testified that the method of treatment in the patents-in-suit was directed at NSCLC with sensitizing mutations. *See, e.g.*, Jury Trial Tr. at 181:15–22 (Weiss testimony) ("Q: Does the definition [of g/e resistant NSCLC] that you applied include people who do not have sensitizing mutations? A: No. It requires that all of these patients would have a sensitizing mutation. Q: And how do you know that? A: Because in order to have received or to be eligible for gefitinib and/or erlotinib, one needs to have a sensitizing mutation."); Jury Trial Tr. at 815:11–20 (Hausheer testimony) ("Q: You mentioned sensitizing mutations. And what's your opinion whether—as to whether gefitinib/erlotinib resistance means the patient has to have sensitizing mutations or not? A: They have to have sensitizing mutations. Q: Why is that? A: Because this is the basis for the gefitinib/erlotinib to be administered to such a patient. These are called sensitizing mutations. So reversible inhibitors will be used, and they're much more effective."); *id.* at 818:7–10. ("Non-small cell lung cancer patients that do not have sensitizing mutations are out of the scope of the claims, and

the specification does not need to describe or enable patients lacking, or any example, lacking sensitizing mutations."). This interpretation is also consistent with the testimony of Dr. Haber, one of the named inventors of the patents-in-suit. *See* Jury Trial Tr. at 296:18–22 (Haber testimony) (explaining that sensitizing mutations "predict[ ] who's going to respond, who's not going to respond. So that's very important because you're not giving drugs to people who won't benefit from them. You can actually be smart about that.").

Wyeth's experts further testified that a POSA would not consider NSCLC with a KRAS mutation or MET amplification to be g/e resistant. *See, e.g.*, Jury Trial Tr. at 181:23–182:1 (Weiss testimony) ("Q: Does the plain and ordinary meaning of gefitinib or erlotinib resistance depend on a specific kind of signaling pathway? A: It depends on the EGFR signaling pathway."); Jury Trial Tr. at 818:16–819:25 (Hausheer testimony) ("KRAS is a separate protein system. The mutations in KRAS are well known. It is independent of the EGFR pathway. And it's just not—it's not part of this. [. . .] KRAS is not a EGFR-mediated pathway. It's bypassing EGFR. It's a different protein system. You know, this is all well-known."); Haber Dep. at 58:05–13 (Q: [P]atients with gefitinib or erlotinib-resistant non-small cell lung cancer that exhibit MET amplification will not obtain a therapeutic benefit from an EGFR inhibitor; correct? A: [. . .] Based on lab experiments, you would predict not, because MET bypasses the entire pathway.").[5] This evidence was more than sufficient for a reasonable jury to conclude that a POSA would not understand "g/e resistant" NSCLC to cover NSCLC without sensitizing mutations, with a KRAS mutation, or with MET amplification. The

[5] This excerpt from Dr. Haber's deposition was presented to the jury at trial.

Court therefore declines to grant judgment as a matter of law for AstraZeneca on this basis.

c. Unit dosage

Lastly, AstraZeneca argues that the patents are not enabled because "an extraordinary and undue amount of experimentation . . . would be required to identify the 'unit dosage' for each of the myriad irreversible EGFR inhibitors encompassed within the scope of the Asserted Claims." Defs.' Post-Trial Mot. at 15. In its view, "[i]dentifying the 'unit dosage' for even just ***a single compound*** is highly unpredictable and involves tremendous amount of work and experimentation, including *in vitro* and *in vivo* tests, tests analyzing a given compound's pharmacokinetics, safety and toxicity studies, and formulation work, all before necessary clinical studies in human patients." *Id.* at 16. Although the patents-in-suit identify ranges for a "unit dosage" of between 1 to 1,000 milligrams for the '314 patent and between 2 to 500 milligrams for the '162 patent, AstraZeneca argues that these ranges are too broad and lacking in guidance for a POSA to determine the "unit dosage" for a given compound. This is particularly problematic, AstraZeneca says, because "the record establishes that for many compounds, including the specification's HKI-272 and EKB-569, many doses—or even the vast majority of doses—within these ranges are toxic." *Id.* at 18–19.

Wyeth responds that "a POSA would know that the desired therapeutic effect is to interfere with the EGFR pathway and 'kill cancer cells'" and that AstraZeneca did not present evidence that the claimed irreversible EGFR inhibitors do not achieve that effect. Pl.'s Resp. at 19. Wyeth argues that AstraZeneca's arguments regarding toxicity, safety, and clinical efficacy seek to add limitations that are not recited in the

asserted claims and that the Court rejected at claim construction. Wyeth further argues that the patents provide sufficient disclosure of "unit dosages" that would achieve the desire therapeutic effect of interfering with the EGFR pathway and killing cancer cells and that determining the dosage for any given irreversible EGFR inhibitor would not require undue experimentation.

Some background on the Court's previous rulings in this case is necessary to navigate the parties' arguments at this stage. At claim construction, the Court stated that the patents define the term "unit dosage" as "physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluents; i.e., carrier, or vehicle." *See Puma Biotech.*, 2023 WL 2683559, at *9 (quoting '314 Patent at 9:33–38). The Court therefore declined to adopt AstraZeneca's proposed construction that would add the words "effective amount" to the definition. *Id.* In ruling on the parties' motions in limine before the jury trial, the Court reiterated that the term "unit dosage" was defined by the specification and that the asserted claims therefore require neither FDA approval nor clinical effectiveness. *See* May 7, 2024 Order on Remaining Motions in Limine at 3–6 [dkt. no. 419]. In other words, the method of treatment described in the patent need not enable a POSA to carry out a successful clinical trial or to gain FDA approval for an irreversible EGFR inhibitor that practices the asserted claims. That is because the scope of the invention, and therefore the scope of what must be enabled, is determined by the patents' claims. In this case, the claims require only that the "unit dosage" "produce[s] the desired therapeutic effect" in a patient. '314 Patent at 9:33–38.

The Court does not agree with Wyeth, however, that the patents are enabled as long as the method of treatment "interfere[s] with the EGFR pathway and 'kill[s] cancer cells.'" Pl.'s Resp. at 19. That is because the patents do not claim "a method for killing cancer cells," or "a method for treating g/e resistant NSCLC," full stop. Rather, the patents claim "[a] method for treating gefitinib and/or erlotinib resistant non-small cell lung cancer *in a patient* in need thereof, comprising administering daily *to the patient* . . . a unit dosage . . . ." '319 Patent at 35:53–57 (emphasis added). The patents therefore must not only enable a unit dosage that produces the desired therapeutic effect, but also a unit dosage that can be *administered daily to the patient*. As Wyeth's expert agreed at trial, there is some level of toxicity—at the extreme, a fatal dose—that could not be administered to a patient. *See* Jury Trial Tr. at 939:24–9:40–5 (Hausheer testimony) ("Q: When you calculate a unit dose, do you make sure that dose is not so high it's going to be toxic to the patient? A: Yeah, you have several unit doses that you're going to use. This is very standard. Q: And so you'll want to avoid administering a toxic dose in order to achieve the desired therapeutic effect, correct? A: Yeah.").

Again, there is no requirement that the patents enable a "unit dosage" that is acceptable in terms of lacking side effects, meeting the FDA's safety criteria, having a particular level of effectiveness against a patient's cancer progression or other clinical symptoms, or meeting any other criteria that might make a drug an attractive option for a practicing clinician. Thus, the fact that an extensive amount of experimentation may be necessary to find an *ideal or optimal* dose is not relevant to the enablement inquiry. But if a POSA would have to undertake undue experimentation to find a "unit dosage" that would not fatally poison a patient, then the patents-in-suit do not enable a POSA to

treat g/e resistant NSCLC in a patient by administering daily a unit dosage to a patient.

Turning to the evidence presented at trial, the specification of the patents indicates that "satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of body weight, optionally given in divided doses two to four times a day, or in sustained release form. The total daily dosage is projected to be from about 1 to 1,000 mg, preferably from about 2 to 500 mg." '314 Patent at 8:60–66. AstraZeneca's expert emphasized that even the narrower range represented a "250-fold range of possible doses." Jury Trial Tr. at 711:2 (Taft testimony). AstraZeneca argues that this broad range of possible doses, standing alone, establishes that the claims are not enabled because a POSA would be required to conduct "substantial additional experimentation," including clinical trials, to determine the correct unit dosage for any given compound. Defs.' Post-Trial Motion at 17. The Court is not persuaded that the mere fact that the specification provides a range of possible dosages renders the asserted claims invalid for lack of enablement. This is particularly so because, as Wyeth points out, AstraZeneca did not provide clear and convincing evidence that "the claimed irreversible EGFR inhibitors do not achieve the desired therapeutic effect—inhibiting EGFR and killing cancer cells." Pl.'s Resp. at 19.

Nevertheless, the Court concludes that AstraZeneca presented clear and convincing evidence such that no reasonable jury could find that the patents-in-suit enabled a POSA to administer a unit dosage of any irreversible EGFR inhibitor covered by the claims *to a patient* without undue experimentation. First, it is undisputed that the specification did not disclose any working examples of unit dosages administered *to*

patients. Although this is not dispositive, it is a relevant factor to consider in the enablement inquiry. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Second, AstraZeneca presented unrebutted evidence that some dosages of compounds within the ranges specified by the patents-in-suit would be toxic to patients, and, more specifically, that the dosage level required for the compounds to be therapeutically effective could be unduly toxic to a patient. *See* Jury Trial Tr. at 650:16–19 (Jänne testimony) (testifying that the dosage ranges described in the patents-in-suit and prior art could "be ineffective and not produce the desired therapeutic effect. It can be too toxic."); *id.* at 681:5–8 (Taft testimony) ("[I]f your toxicity threshold is here and you have to give a much higher dose in order to get activity, you don't have a therapeutic window, and that means you will not achieve a therapeutic effect."); *id.* at 711:6–9 (Taft testimony) ("And it's highly likely, not only if there was a unit dose within that range, there may also be a toxic dose within that range too. You just don't know. The patents really don't provide any guidance on that."). This included evidence that dosages within the specified ranges for two of the compounds specifically identified in the patents, HKI-272 and EKB-569, would be unduly toxic to patients. *See id.* at 707:22–708:18 (Taft testimony) ("Q: What are the named inventors and their co-authors describing about their preclinical research of HKI-272 in this article? A: Well, what they're describing is that those in vitro, like, test-tube-type experiments were done using a concentration of one micromole per liter. But they go on to say when they actually put it into people the highest concentration that they could achieve without causing toxicity was .2. So you're looking at least a five-fold difference between those values. And . . . I was discussing this concept of therapeutic range it's important that whatever the threshold is above

which you're going to have toxicity, you have to make sure your active concentration is in that—below that window and below that threshold. This is the opposite. In this case, what you're talking about is that the concentrations where you're going to have toxicity is .2, but they were saying that what they found is that five-fold higher is where you need activity. What that means is there is no therapeutic range, at least based on this statement for HKI-272, which also means there's not a unit dose for that compound."); *id.* at 943:2–944:1 (Hausheer testimony) ("What the named inventors said in 2008 is using the maximum tolerated dose [of HKI-272], you couldn't effectively inhibit T790M. That's what they said, correct? A: That's what they said." [. . .] Q: Now the maximum tolerated dose of EKB-569 is even lower, is it not? A: I believe so. Q: Okay. So the problem is—so—and we don't even know for the third [compound disclosed in the specification], HKI-357, what the maximum tolerated dose is, correct? A: No."); Jury Trial Tr. at 336:1–337:1 (Haber testimony) ("Q: So at this time in April of 2005, after you filed your patent application in February, you don't know how much of HKI-272 can be therapeutically administered to patients, correct? You don't know? […] A: Yes. [. . .] Q: And, in fact, you later found out, correct, that the concentrations that you were studying and reporting in your patent were five times higher than the maximum tolerated dose for HKI-272, correct? A: Yes.").

Wyeth did not provide any evidence to rebut AstraZeneca's evidence that some dosages of irreversible EGFR inhibitors that fall within the claims could be toxic if administered to patients. Thus, a POSA would be required to test different possible irreversible EGFR inhibitors to identify whether the dosage levels necessary to produce the desired therapeutic effect would be toxic if administered. *See* Jury Trial Tr. 711:6–9

(Taft testimony) ("[I]t's highly likely, not only if there was a unit dose within that range, there may also be a toxic dose within that range too. You just don't know. The patents really don't provide any guidance on that."). In scenarios where there is no non-toxic therapeutic range for a given compound, a POSA would not be able to practice the claimed method of treatment in the patient.

Although the existence of some inoperative embodiments does not necessarily render a patent invalid, *see Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380 (Fed. Cir. 2002), that is only so if a POSA need not engage in undue experimentation to cull out inoperative embodiments. *See Atlas Powder Co. v. E.I. du Pont De Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984). The Supreme Court's decision in *Amgen* makes clear that although "a specification may call for a reasonable amount of experimentation to make and use a patented invention," courts "in allowing that much tolerance . . . cannot detract from the basic statutory requirement that a patent's specification describe the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art' to 'make and use' the invention." *Amgen Inc.*, 598 U.S. at 612 (quoting 35 U.S.C. § 112(a)). Although the Supreme Court declined to establish bright-line rules regarding what a specification must disclose in order to enable patents that claim "an entire class of processes, machines, manufactures, or compositions of matter," the Court suggested that the patent must provide *some* guidance that will "reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset." *Id.* at 611. For example, the Supreme Court cited to *Wood v. Underhill*, 46 U.S. 1 (1847), in which it concluded that a patent that "claimed a process for making bricks" was enabled because it "included 'a general rule' about the

proportion of dust and clay to use and offered two alternative proportions 'where the clay has some peculiarity.'" *Amgen Inc.*, 598 U.S. at 611 (quoting *Wood*, 46 U.S. at 5). In contrast, the Supreme Court cited to *The Incandescent Lamp Patent*, 159 U.S. 465 (1895), in which it held that a patent for an "electric lamp with an incandescing conductor made of carbonized fibrous or textile material" was not enabled because "the record showed that most fibrous and textile materials failed to work" and the patent did not "disclose[ ] a quality common to fibrous and textile substances that made them peculiarly adapted to incandescent lighting." *Amgen Inc.*, 598 U.S. at 608 (quoting *Incandescent Lamp*, 159 U.S. at 608–09 (internal quotation marks omitted)). Similarly, the Court held that the patent at issue in *Amgen*, which claimed a class of functionally-defined antibodies, was not enabled because it "call[ed] on scientists to create a wide range of candidate antibodies and then screen each to see which happen to [exhibit the desired functional effect]" without "identif[ying] a quality common to every functional embodiment." *Id.* at 614.

Here, the patents-in-suit do not teach which unit dosages of compounds covered by the claims could be administered daily to a patient and which could not. Thus, the patents-in-suit provide "only a starting point, a direction for future research" that places the burden on a POSA to conduct "an iterative, trial-and-error approach to practice the claimed invention." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 939–41 (Fed Cir. 2010) (quoting *Automotive Techs. Int'l, Inc. v. BMW of N.A., Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007)). Nor can this experimentation be said to be merely routine where the patents-in-suit provide no guidance that would help a POSA *reliably* screen between compounds that would have the desired therapeutic effects at toxic versus non-toxic

dosage ranges. *See Amgen Inc.*, 598 U.S. at 614 (finding the patent-in-suit invalid for lack of enablement where specification "called on scientists to create a wide range of candidate antibodies and then screen each to see which happen to [exhibit the desired functional effect]"). Instead, a POSA would have to conduct further experimentation unassisted by the patents-in-suit. This renders the claims insufficient to meet the enablement requirement. *See ALZA Corp.*, 603 F.3d at 943 ("Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."). Stated differently, this case is more like *Incandescent Lamp* and *Amgen* than *Wood.* For these reasons, the Court concludes that AstraZeneca presented clear and convincing evidence such that no reasonable jury could find that the patents-in-suit enabled a POSA to administer a unit dosage of any irreversible EGFR inhibitor covered by the claims to a patient without undue experimentation. The Court therefore concludes that the asserted claims of the '314 and '162 patents are invalid for failure to meet the enablement requirement of 35 U.S.C. § 112(a).

4. Written description

Although the Court has concluded that AstraZeneca is entitled to judgment as a matter of law on the issue of enablement and therefore that the patents-in-suit are invalid, the Court will nevertheless address the remainder of the parties' arguments for the sake of completeness.

AstraZeneca further argues that judgment as a matter of law should be entered in its favor because the asserted claims are invalid for lack of written description. A patent specification must contain a written description that "clearly allow[s] persons of

ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc.*, 598 F.3d at 1351 (quoting *Vas–Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). "The test for the sufficiency of the written description 'is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.'" *Vasudevan Software, Inc.*, 782 F.3d at 682 (quoting *Ariad Pharms., Inc.*, 598 F.3d at 1351). This is a question of fact. *Id.* "A party must prove invalidity for lack of written description by clear and convincing evidence." *Id.* (quoting *Laryngeal Mask Co. Ltd. v. Ambu*, 618 F.3d 1367, 1373–74 (Fed. Cir. 2010)).

As the Court discussed in its decision on AstraZeneca's motion for summary judgment, "the asserted claims encompass not just a method of treatment with *specific* irreversible EGFR inhibitors defined by their structure but rather a method of treatment with the entire *class* of irreversible EGFR inhibitors that are capable of performing a specific *function*." *Puma Biotech.*, 2024 WL 1157120, at *8. The Federal Circuit has explained in the analogous (though not identical) context of patents claiming a functionally-defined genus of compounds that "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (quoting *Ariad Pharms., Inc.*, 598 F.3d at 1350).

AstraZeneca's arguments with respect to written description mirror its arguments with respect to enablement. It argues that the patents-in-suit fail to provide adequate

description of (1) every irreversible EGFR inhibitor claimed to practice the claimed method of treatment; (2) the treatment of all types of g/e resistant NSCLC; and (3) every unit dosage of the claimed inhibitors.

a. Any compound

As the Court discussed with respect to AstraZeneca's enablement argument, the parties presented conflicting evidence regarding the representativeness of the three compounds disclosed in the specification and whether the specification, viewed in light of the state of the art at the time the patent was filed, would allow a POSA to "visualize or recognize" the compounds that can be used to practice the claims. *Id*. For these same reasons, AstraZeneca is not entitled to judgment as a matter of law on its written description defense. AstraZeneca attempts to distinguish "pyrimidine-based irreversible EGFR inhibitors (containing a pyrimidine core) that are characteristic of the so-called 'third generation' inhibitors like osimertinib [Tagrisso] and others," which it argues are not represented by the "second generation" inhibitors described by the patents-in-suit. Defs.' Post-Trial Mot. at 22. But Wyeth's expert testified that Tagrisso and other third-generation inhibitors did not have meaningfully different structural features compared to the example compounds and structures disclosed in the specification. *See* Jury Trial Tr. at 979:5–981:1 (Jorgensen testimony). The jury was not obligated to credit AstraZeneca's evidence over Wyeth's. AstraZeneca also argues that the specification "does not describe the wild-type sparing, 'mutant selective' profile of third generation EGFR inhibitors" such as Tagrisso and therefore it is "functionally different than what the patents-in-suit describe." Defs.' Post-Trial Mot. at 22–23 (emphasis omitted). But the fact that Tagrisso may have some additional characteristic that makes it particularly

effective does not mean that it does not share the basic features of the so-called second-generation irreversible EGFR inhibitors disclosed in the patents-in-suit. Further, there is simply no requirement that the specification describe each and every compound that might be used to practice the claimed method of treatment. *See Amgen Inc.*, 598 U.S. at 610–11 (stating that a specification need not always "describe with particularity how to make and use every single embodiment within a claimed class").

b. g/e resistant NSCLC

Similarly, AstraZeneca argues that the specification does not adequately describe a method of treating NSCLC lacking sensitizing mutations, NSCLC with a KRAS mutation, and NSCLC with MET amplification. As discussed, however, Wyeth presented ample and persuasive evidence that a POSA would not consider these types of NSCLC to be g/e resistant. AstraZeneca therefore is not entitled to judgment as a matter of law on this basis.

c. Unit dosage

Lastly, AstraZeneca asserts that the patents-in-suit "fail to demonstrate possession of the 'unit dosage' of even a single irreversible EGFR inhibitor, much less the full scope of claimed 'unit dosages.'" Defs.' Post-Trial Mot. at 24 (emphasis omitted). The Court agrees that the patents-in-suit do not contain a written description that "clearly allow[s] persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed," i.e. a unit dosage of an irreversible EGFR inhibitor that can be administered daily to patient. *Ariad Pharms., Inc.*, 598 F.3d at 1351 (quoting *Vas–Cath Inc.*, 935 F.2d at 1563). Although the specification discusses a suggested range for a unit dosage between 2 and 500 milligrams per day, nothing in the specification

suggests that the inventors in fact had identified a unit dosage of the specified compounds that could be administered daily to a patient at levels high enough to show the desired therapeutic effect of interfering with the EGFR pathway and killing cancer cells. Instead, as the Court discussed with respect to enablement, a POSA would be required to engage in significant experimentation to determine an administrable unit dosage—if any—for different compounds covered by the asserted claims. Again, the patents-in-suit perhaps contain a sufficient written description of a process for disrupting EGFR pathways and eliminating cancer cells, but that is not the extent of what the patents claim. With respect to a method of treatment involving administering daily a unit dosage to a patient, the specification describes an unfinished project, not a completed invention. For these reasons, the Court concludes that AstraZeneca is entitled to judgment as a matter of law that the patents-in-suit are invalid for lack of written description.

C. Damages

Finally, AstraZeneca argues that it is entitled to judgment as a matter of law that Wyeth did not suffer any damages. It asserts that the jury's award of $107.5 million in damages was "premised on a legally insufficient basis" for two reasons. Defs.' Post-Trial Mot. at 30. First, it asserts Wyeth did not present sufficient evidence regarding the "royalty base." *Id.* AstraZeneca does not expand on this argument but rather refers back to the portion of its brief discussing infringement. The Court therefore assumes that AstraZeneca is referring to its argument that it did not induce infringement as to all three indications of Tagrisso. As the Court discussed above, there was sufficient evidence for the jury to conclude that AstraZeneca induced infringement with respect to

all three indications of Tagrisso. Because AstraZeneca does not articulate any other argument with respect to the "royalty base," the Court declines to grant it judgment as a matter of law on this basis.

Second, AstraZeneca argues that "Wyeth's evidence on royalty rate is also insufficient" because Wyeth's expert, Dr. Mohan Rao, "based his opinion as to royalty rate on his analysis of six BioSci database licenses" but "did not perform the baseline comparability analysis required to provide a legally sufficient basis for his opinion based on these licenses." *Id.* AstraZeneca raised this precise argument, however, in support of its motion to exclude Dr. Rao's testimony. The Court previously concluded "that Dr. Rao has established the 'baseline comparability' of the six licenses at issue and the patents-in-suit." *See Puma Biotech., Inc.*, 2024 WL 1157120, at *22. And his testimony at trial was likewise sufficient. AstraZeneca does not articulate any reason why the Court should reconsider its conclusion with respect to baseline comparability, nor does it provide additional arguments regarding the insufficiency of the evidence beyond its renewed baseline-comparability argument. Furthermore, at trial, Dr. Rao's testimony was not based exclusively or even primarily on the disputed BioSci database licenses. To the contrary, he testified that he used a license agreement involving the patents-in-suit between Pfizer and Puma Biotechnologies as the "starting point" for his analysis. *See* Jury Trial Tr. at 357:13–361:16 (discussing his analysis of the Pfizer-Puma license and the adjustments needed to account for differences between that license and the hypothetical license at issue in this case). In addition, AstraZeneca's own damages expert, Carla Mulhern, testified that a reasonable royalty rate, after correcting for errors in Dr. Rao's analysis, would be three percent. *See* Jury Trial Tr. at 768:10–13 (Mulhern

testimony) ("And so based on my analysis, if we adjusted for those flaws, some of those flaws, that would result in a revised or adjusted royalty rate of 3 percent rather than the 7.1 percent that Dr. Rao testified about."). This is quite close to the implied royalty rate of 3.5 percent that would result in the $107.5 million in damages awarded by the jury. AstraZeneca therefore is not entitled judgment as a matter of law on this basis.

Conclusion

For the reasons discussed above, the Court grants AstraZeneca's motion for judgment as a matter of law [dkt. no. 483] that the patents-in-suit are invalid due to lack of enablement and lack of written description of the claimed invention but otherwise overrules AstraZeneca's motion. The Court will cause entry of an amended judgment accordingly. The Court denies as moot Wyeth's motion under Federal Rule of Civil Procedure 59(e) for supplemental damages, interest, and ongoing royalties [dkt. no. 494].

MATTHEW F. KENNELLY
United States District Judge

Date: August 14, 2024