No. 2019-2156

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GENENTECH, INC.,

Plaintiff-Appellant,

CITY OF HOPE,

Plaintiff,

v.

AMGEN INC.,

Defendant-Appellee.

On Appeal from the United States District Court
for the District of Delaware, No. 1:18-cv-00924-CFC, Judge Colm F. Connolly

NON-CONFIDENTIAL PLAINTIFF-APPELLANT GENENTECH, INC.'S EMERGENCY MOTION FOR AN INJUNCTION PENDING RESOLUTION OF APPEAL AND MOTION TO EXPEDITE BRIEFING ON APPEAL

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CONFIDENTIAL MATERIAL OMITTED

The confidential information that has been deleted on pages 2-4, 6, 9-11, 13, 15, 17, 19-20, 22-23 and Exhibits 2-3, 12-13, 17-24, and 28-31 describes highly confidential, competitively sensitive information relating to the Herceptin biosimilars market including market entry, forecast planning, competitive intelligence, and the terms of third party license agreements.

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Pursuant to Federal Rule of Appellate Procedure 8, Plaintiff-Appellant Genentech, Inc. ("Genentech") submits this motion for an emergency injunction to maintain the status quo by preventing Appellee Amgen Inc. ("Amgen") from imminently launching its biosimilar of Genentech's biologic breast cancer therapy Herceptin pending resolution of this appeal. Genentech further requests expedited briefing of both this motion and this appeal, and will submit its principal brief within seven days. Pursuant to Rule 27(a)(5), counsel for Genentech informed counsel for Amgen of Genentech's intent to seek the requested relief and sought Amgen's position. Amgen indicated that it would oppose such a motion and Genentech assumes it will file an opposition.

INTRODUCTION

Amgen issued a press release last night announcing that it is launching at risk a biosimilar version of Genentech's Herceptin drug, called "Kanjinti."[1] That imminent launch is in violation of Genentech's patent rights; indeed, Amgen has not disputed infringement, and the infringed patents were upheld by the PTAB following full IPR trials over the same obviousness arguments that Amgen is advancing in this litigation.

[1] *See* Ex. 1, Amgen Press Release, available at https://www.amgen.com/media/news-releases/2019/07/amgen-and-allergans-mvasi-bevacizumabawwb-and-kanjinti-trastuzumabanns-now-available-in-the-united-states/.

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Unless enjoined, Kanjinti's launch will have immediate and irreversible consequences. Genentech seeks this emergency relief to preserve the status quo before the opportunity is lost to Amgen's immediate efforts to come to market. Genentech will undisputedly suffer irreparable price erosion and lost market share due to Amgen's infringement. There is a causal nexus between Amgen's infringement and those irreparable injuries because the inventions claimed by Genentech's patents are commercially significant—by Amgen's own estimation, they cover [redacted] of patient use. Indeed, after the validity of Genentech's patents was upheld in IPRs, [redacted]. If Amgen's launch is allowed to proceed, Genentech will never be able to be placed back into the place it would have been had its patent rights been respected. An injunction maintaining the status quo therefore is the only way that Genentech can obtain effective relief.

The district did not disagree with any of this. Instead, it denied Genentech a preliminary injunction for two reasons.

First, it held that Genentech had not demonstrated irreparable harm because Genentech had supposedly delayed in seeking injunctive relief. But Amgen undisputedly only decided to launch at risk on [redacted], and Genentech filed its

motion for a preliminary injunction [redacted] days later. The district court faulted Genentech for not seeking injunctive relief when Amgen provided its notice of commercial marketing under 42 U.S.C. § 262(*l*)(8) on May 15, 2018. But Genentech's motion for injunctive relief would not have been ripe at that time. There was no immediate threat of launch because Kanjinti was not approved by the FDA until thirteen months later. And Amgen's product remained in flux up until the point of FDA approval. For example, [redacted]. And although Amgen provided discovery to Genentech earlier this year indicating that it intended to be "ready" to launch in July 2019, Amgen repeatedly represented that it had not actually decided that it would launch—including in a brief filed with the district court on June 26, 2019. Amgen only decided to launch on [redacted], and Genentech filed its motion for a preliminary injunction as soon as it learned of those plans [redacted] days later.

Second, the district court held that Genentech could not demonstrate irreparable harm because Genentech had licensed its patents to other biosimilar manufacturers in settlement of litigation. In doing so, the court applied a categorical rule that licenses demonstrate the absence of irreparable harm in violation of *eBay* and this Court's precedents. None of Genentech's licensees are

even currently licensed to launch in the United States; the first licensed launch will be in [redacted]. And if anything, Genentech's licenses reflect that the inability to place a monetary value on a license. These licenses show that Genentech negotiated for an [redacted], because Genentech did not think the harm of entry could be compensated with money damages. The district court's conclusion that Genentech forfeited its right to obtain an injunction would mean, as a practical matter, that innovators cannot settle biosimilar cases without losing their right to exclude, making settlement effectively impossible. That, too, sets a new standard requiring reversal. These errors infected the District Court's truncated analysis of Genentech's motion for a TRO and a preliminary injunction. The district court failed to consider undisputed evidence of irreparable harm, failed to address Genentech's likelihood of success on the merits or the balance of hardships, and addressed the public interest in a footnote.

Given these errors in the district court's analysis, coupled with Genentech's strong showing on the merits, Genentech is entitled to an injunction that bars Amgen from launching its biosimilar product pending the outcome of this appeal. Otherwise, Amgen's infringing launch of Kanjinti during this appeal will irreversibly alter the marketplace, causing harm to Genentech in multiple ways that money damages or later injunctive relief could never fully compensate, a proposition that Amgen itself does not dispute.

BACKGROUND

Genentech invented and developed Herceptin, the first-of-its-kind biologic therapy that specifically targets a protein associated with an aggressive form of breast cancer. Herceptin was the first therapy that delayed cancer progression and, in many patients, provided a cure. Ex. 2, Tannenbaum Decl. ¶¶6-9, 12, 22. After developing Herceptin, Genentech invested billions of dollars in research to improve therapeutic options with Herceptin, resulting in further innovations. Ex. 3, Oliger Decl. ¶7. For example, Genentech discovered that Herceptin could be dosed less frequently than the approved weekly dosing regimen without compromising effectiveness. This inventive extended-interval dosing is described and claimed in Genentech's U.S. Patent Nos. 6,627,196, 7,371,379, and 10, 160,811 ("the Dosing Patents"). Exs. 4-6. It also is reflected in the current Herceptin label reciting a dosing regimen for early breast cancer patients of an initial dose of 8 mg/kg, followed by subsequent doses of 6 mg/kg every three weeks ("8/6 three-weekly dosing"). Ex. 7 at GNE-HER_002466538. Two of the Dosing Patents (the '196 and '379 patents) were challenged in IPRs, and their validity was upheld. Exs. 8-11. The other Dosing Patent (the '811 patent) is narrower than the '196 and '379 patents, and issued after the IPRs were completed.

Seeking to profit from Genentech's groundbreaking work, in May 2018 Amgen gave Genentech Notice of Commercial Marketing of its Herceptin

biosimilar called "Kanjinti," resulting in Genentech filing the underlying patent infringement action. During the pendency of this action, it was unclear when or if Amgen would launch its biosimilar before the December 9, 2019 trial date. During the approval process, [redacted], and even after FDA approval on June 13, 2019, Amgen repeatedly asserted that it had not made a launch decision.

But in July 2019, Genentech received concrete market intelligence indicating that Amgen was planning an imminent launch of Kanjinti within days. In an effort to protect its extensive investments and valuable patent rights from Amgen's infringement, Genentech filed with the district court an emergency motion in which it asked the Court to temporarily restrain and preliminarily enjoin Amgen from launching Kanjinti. In its supporting papers, Genentech contended that: (1) without an injunction, Genentech would suffer loss of market share, price erosion, and reputational injury resulting directly from Amgen's infringement that cannot be addressed with money damages; (2) Genentech is likely to prevail on the merits inasmuch as [redacted], and Amgen's defense hinges on essentially the same invalidity arguments that the Patent Office recently rejected in multiple IPRs; (3) unlike the significant and permanent harm facing Genentech, Amgen will lose no customers or market share if forced to wait until the issues are resolved in the December trial; and (4) patient access would not

be affected because Genentech ensures that patients can obtain Herceptin regardless of ability to pay.

Although the district court initially ordered a standstill, after receiving full briefing, at 5:24 p.m. Eastern on July 18, 2019, the district court issued an order denying Genentech's motions for injunctive relief. Ex. 15. Genentech sought Amgen's agreement not to launch pending decision on emergency motions for preliminary injunction but Amgen refused. That evening, Amgen issued a press release announcing that Kanjinti is now available for sale in the United States. Ex. 1. Genentech filed an emergency motion with the district court this morning (Exs. 12, 13), which Amgen responded to by indicating that it will "respond by Monday, July 23." Ex. 14. The district court held a telephonic hearing on Genentech's Rule 62(d) motion on July 19, 2019 and denied that motion in an oral order at the conclusion of the hearing at 4:45 p.m. Eastern.

In the interim, Amgen's press release suggests that Kanjinti is now available for sale, and Genentech cannot wait to obtain relief. Unless preliminarily enjoined, Amgen's launch will irreversibly alter the market for Herceptin and irreparably harm Genentech. To prevent this disruption to the status quo, Genentech requests that this Court enter an injunction during the appeal pursuant to Rule 8.

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). The district court's Order of July 18, 2019 denied Genentech's motion for a

preliminary injunction. Ex. 15. Genentech timely appealed from the district court's Order. Ex. 16. This Court has jurisdiction pursuant to 28 U.S.C. § 1292(a)(1) and (c)(1).

ARGUMENT

I. THE COURT SHOULD GRANT GENENTECH'S REQUEST FOR AN INJUNCTION PENDING APPELLATE REVIEW

This Court has the discretion to grant an injunction pending appeal. *Astrazeneca LP v. Breath Ltd.*, 2013 WL 9853383, at *1 (Fed. Cir. May 24, 2013). In deciding whether to grant such an injunction, the Court considers "(1)whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies." *Standard Havens Prods., Inc. v. Gencor Indus., Inc.*, 897 F.2d 511, 512 (Fed. Cir. 1990) (quoting *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987)). The analysis is flexible, and the Court should "assess[] the movant's chances for success on appeal and weigh[] the equities as they affect the parties and the public." *Id.* (quoting *E.I. DuPont de Nemours & Co. v. Phillips Petroleum Co.*, 835 F.2d 277, 278 (Fed. Cir. 1987)).

As explained below, Amgen's at-risk launch as the first Herceptin biosimilar would cause immediate irreparable harm to Genentech. Amgen did not dispute that its launch will cause Genentech price erosion and loss of market share.

Genentech's evidence of irreparable harm, combined with Amgen's concession of [redacted] and Genentech's unrebutted evidence of validity (an issue on which Amgen has the burden) powerfully supports granting Genentech relief. Indeed, the relief Genentech requests here is the same relief Amgen obtained from this Court when it was the "reference product sponsor" and was denied preliminary injunctive relief. *See Amgen, Inc. v. Sandoz, Inc.*, 2015-1499, D.I. 105 (Fed. Cir. May 5, 2015).

A. Genentech Overwhelmingly Demonstrated Its Entitlement To Injunctive Relief.

Genentech is likely to succeed on the merits of its appeal because the district court's denial of the preliminary injunction was based on errors of law. Genentech showed that it was likely to succeed on the merits of its infringement case.

1. The district court misconstrued the law on irreparable harm.

Rather than address Genentech's essentially undisputed evidence of price erosion and lost market share, the district court found that those factors need not be considered because Genentech purportedly delayed seeking injunctive relief and licensed other Herceptin biosimilars. The district court's reasoning sets a problematic and impractical precedent that is not supported in law.

First, the district court created an unsupported standard that Genentech's purposed delay negates irreparable harm. Indeed, the start of Genentech's

purposed delay is unclear. The district court found that "Genentech has known of Amgen's intent to market Kanjinti since Amgen served its 180-day Notice of Commercial Marketing on May 15, 2018," that by February 2019 Genentech understood that the FDA would act on Amgen's resubmission by the end of June 2019, and that Amgen documents produced in April 2019 indicated that Amgen planned to launch in July 2019. Ex. 17 at 5.

To the extent the district court implicitly determined that Genentech was required to have moved either (1) as soon as Amgen sent the 42 U.S.C. § 262(*l*)(8) notice of commercial marketing in May of 2018 or (2) sometime prior to Amgen's receiving FDA approval in late June of 2019, the facts of this case establish that rule's impracticality. During FDA review, [redacted]. Ex. 18, 232:9-24, 234:5-24, 239:10-240:10; Ex. 19, 179:5-14, 179:24-180:4, 202:3-19; Ex. 20; Ex. 21. [redacted]. Ex. 22 at 219:2-25. Amgen's [redacted] implicated the patent claims and theories of infringement. Had Genentech moved for a preliminary injunction on the dosing patents when Amgen filed its (*l*)(8) notice, Amgen could have defeated that motion

simply [redacted]. The district court's ruling would force plaintiffs to file—and the courts to address—motions for preliminary injunction even absent a present need for injunctive relief and even when changes in the biosimilar product would potentially moot the preliminary injunction analysis, would waste court and party resources, and is contrary to the requirement of an imminent, irreparable injury necessary to obtain a preliminary injunction.

To the extent the district court implicitly determined that Genentech should have filed when it learned that Amgen had been planning a July "launch readiness" date, that too would essentially force plaintiffs to file prematurely. Amgen itself stressed, even after approval, that it had made no launch decision and that launch "may not be ripe." Ex. 23 31:4-11 ("So it may not be ripe. It's all future activity."); *see also id.* at 30:3-8 (actual launch might occur "two months," "six months," or even "a year" later). It is undisputed that Amgen made no actual decision to launch until [redacted]. Ex. 24, Jacobson Decl. ¶5; *see* Ex. 23 29:10-17 (Amgen's counsel distinguishing between being ready to launch and launching). Genentech filed its motions just two days after Amgen's launch decision.

Genentech is not aware of any cases finding that a party in Genentech's position is required to seek injunctive relief where the product is in flux and launch is undetermined. Rather, the cases cited by the district court, *Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364 (Fed. Cir. 2005), *Polymer Techs., Inc. v.*

Bridwell, 103 F.3d 970 (Fed. Cir. 1996), are inapplicable because they did not find undue delay (and the defendants had already launched their products). *See Pfizer*, 429 F.3d at 1371, 1382 (filing suit two months after infringer's launch and nearly two years after notice of the defendant's assertion of noninfringement not undue delay); *Polymer Techs.*, 103 F.3d at 976 (party not required to sue "absent evidence of … infringing activities," which "did not commence until roughly four months before [patent holder] brought this suit"). The district court's reliance on *Amgen Inc. v. Apotex Inc.* for the proposition that the BPCIA's 180-day notice requires an early motion for preliminary injunction is similarly misplaced. That case was decided before the Supreme Court's decision in *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017). Pre-*Sandoz*, the benefit of the 180-day rule espoused by *Amgen Inc. v. Apotex Inc.* depended on the idea that the 180-day notice must issue ***after FDA approval*** of the biosimilar. 827 F.3d 1052, 1062 (Fed. Cir. 2016) ("[W]e read (8)(A) as allowing the 180-day notice of commercial marketing to be sent as soon as the license issues, even if it is not yet effective, because it is at the time of the license that 'the product, its therapeutic uses, and its manufacturing processes are fixed.'"). It therefore did not contemplate the situation here, where the scope of potential infringement remained undetermined months after the (*l*)(8) notice was served.

Second, the district court found that Genentech licensing other biosimilars negates irreparable harm without considering the circumstances of those prior licenses—effectively adopting a categorical rule that past licensing defeats irreparable harm in violation of *eBay*. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 393-394 (2006). In settling with other biosimilar applicants, Genentech relied on this Court's precedents that "the fact that a patentee has licensed others under its patents does not mean that unlicensed infringement must be permitted while the patents are litigated." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008). Indeed, this Court has reversed denials of injunctions based on the district court's failure to examine the differences between previously licensed parties and the party sought to be enjoined. *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1370 (Fed. Cir. 2013) ("[T]he district court's focus on Apple's past licensing practices, without exploring any relevant differences from the current situation, hints at a categorical rule that Apple's willingness to license its patents precludes the issuance of an injunction," which is inconsistent with the Supreme Court's decision in *eBay*).

The licenses at issue here carry [redacted]. Instead, Genentech [redacted], and entered into those agreements ***to settle litigation and because Genentech could not put a price on a license***. In this situation, the licenses simply do not indicate that any harm from Amgen's launch is

compensable in damages. *See Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, No. 04 C 5312, 2008 WL 4531371, at *4 (N.D. Ill. May 22, 2008), *aff'd*, 595 F.3d 1340 (Fed. Cir. 2010) (finding that the inadequate remedy at law factor in a permanent injunction analysis favored plaintiff where its past licenses "were negotiated in exchange for the parties' agreement to settle, rather than litigate."); *Abbott Labs. v. Sandoz, Inc.*, 500 F. Supp. 2d 807, 843 (N.D. Ill. 2007), *aff'd*, 544 F.3d 1341 (Fed. Cir. 2008) (settlement agreements allowing two specific generic drugmakers to enter the market the following year did not mean that patent holder gave up its right to exclude generics in the present).

The two cases cited by the district court are not applicable. In *Polymer Techs, Inc. v. Birdwell*, 103 F.3d 970, 975 (Fed. Cir. 1996), there were no licenses at issue; that case merely cites the second case the Court relies upon, *High Tech Medical Instrumentation, Inc. v. New Image Industries, Inc.*, 49 F.3d 1551, 1557 (Fed. Cir. 1995), for the proposition that a party's licensing history can be a factor. High Tech, in turn, took the patentee's "apparent willingness to grant a [royalty-bearing] license under its patent" to the defendant in that case—not a third party—into account as one of many factors weighing against injunctive relief. *Id.* *High Tech* is further distinguishable because the patentee was a non-practicing entity—"the lack of commercial activity by the patentee" was a "significant factor" in the analysis. *Id.* at 1556.

Under the district court's ruling, a patent owner would be barred from obtaining injunctive relief where it has licensed to other parties, irrespective of whether those parties have products on the market and without regard to whether the licenses reflect a willingness of the patent holder to accept money. Such a rule would make litigation settlements in the pharmaceutical area essentially impossible, since a patentee could never settle litigation by permitting licensed entry, even at a future date, without effectively allowing immediate entry to anyone else who chooses to launch at risk. That result is contrary to the strong policy in favor of settlement.

2. Genentech Is Likely to Succeed on the Merits.

The district court did not even consider whether Genentech was likely to succeed in ultimately proving infringement. But this factor should have weighed strongly in favor of Genentech—indeed, [redacted].

As to validity, at the preliminary injunction phase, "the very existence of the patent satisfies [the patentee's] burden on validity." *Purdue Pharma L.P. v. Boehringer Ingelheim,* GMBH, 237 F.3d 1359, 1365 (Fed. Cir. 2001). To prevail, Amgen was required to show "evidence of invalidity [that] is sufficiently persuasive that it is likely to overcome the presumption of patent validity." *PPG Indus., Inc. v. Guardian Indus. Corp.,* 75 F.3d 1558, 1566 (Fed. Cir. 1996).

Amgen failed to carry this burden. Amgen presented no expert evidence and instead recycled arguments already rejected by the PTAB under a lower standard of proof. That was insufficient to raise a substantial question as to validity. Indeed, in a case like this involving a complex technology, expert testimony is critical to the proof of obviousness. *See, e.g.*, *Allergan, Inc. v. Barr Labs., Inc.*, 501 F. App'x 965, 972 (Fed. Cir. 2013). And the PTAB's reasoned analysis in final written decisions rejecting the obviousness theories that Amgen is advancing in this litigation confirms that Genentech has a reasonable likelihood of success on the merits. Exs. 8-11.

B. Genentech Will Be Irreparably Harmed Absent An Injunction.

1. Genentech will suffer irreparable harm.

By launching at risk, Amgen will cause incalculable harm to Genentech. Amgen will be the only Herceptin biosimilar on the market; absent an injunction, Amgen's infringement will cause Genentech to suffer price erosion and lost market share. *See, e.g.*, *Abbott Labs.*, 544 F.3d at 1361-1362 (listing categories of harm, including price erosion and loss of market share).

These harms are familiar to Amgen—it has embraced each of them in its own efforts to prevent drug manufacturers from entering the market and competing with Amgen's own reference drugs. Ex. 25 at 14-15; Ex. 26 at 12-13; Ex. 27 at 19. Indeed, Amgen is in a powerful position as both an innovator and a biosimilar

manufacturer because it can leverage existing relationships with customers, enhancing each of the harms described below. Ex. 3, Oliger Decl. ¶53; Ex. 28, Jena Decl. ¶59.

a. Price erosion

Amgen's launch of Kanjinti will cause price erosion by forcing Genentech to decrease the amount it can charge for Herceptin. *E.g.*, *Celsis in Vitro, Inc. v. Cellzdirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012) (collecting cases wherein price erosion constitutes irreparable harm). Specifically, Amgen expects to set Kanjinti's net price at a [redacted] discount to Herceptin through 2028. Ex. 29, AMGKAN02926063; Ex. 28, Jena Decl. ¶58. To maintain customers, Genentech will have to lower its effective net price for Herceptin, add rebates, and adjust contracts, resulting in a significant loss of revenue. Ex. 3, Oliger Decl. ¶¶48-52; Ex. 28, Jena Decl. ¶58.

That price erosion will be irreversible because Genentech will not be able to recoup loss with future, higher prices or reduced discounts. Ex. 28, Jena Decl. ¶99-101; *see Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (irreparable harm due to "irreversible price erosion"); *see also Momenta Pharms., Inc. v. Amphastar Pharms., Inc.*, 882 F. Supp. 2d 184, 197 (D. Mass. 2011) ("'Requiring purchasers to pay higher prices after years of paying lower prices to infringers is not a reliable business option.'"). The harms from Amgen's entry

would continue even if Amgen were later removed from the market because Genentech would be unable to raise prices to pre-entry levels. Ex. 28, Jena Decl. ¶99-101.

The specific harm to Genentech as a result of price erosion is difficult to quantify. Genentech's responses to Amgen's entry will be multi-faceted and complex, and the specific effects of Amgen's activity will be difficult to unravel from other market conditions. Ex. 28, Jena Decl. ¶¶65-67. *See Sanofi-Synthelabo*, 470 F.3d at 1372 ("complex pricing scheme" for prescription drugs means additional entrants have potential to irreversibly erode prices in unpredictable ways); *Hoffmann-La Roche Inc. v. Cobalt Pharms. Inc.*, 2010 WL 4687839, at *12 (D.N.J. Nov. 10, 2010). This is so even after other trastuzumab biosimilars enter the market, as isolating the impact of Kanjinti as opposed to other biosimilars on the price of Herceptin will be even more complex. Ex. 28, Jena Decl. ¶¶70-72. In addition, Genentech has other related products for the treatment of HER2-positive breast cancer that will be adversely affected by Amgen's launch of Kanjinti—further reinforcing the irreparable harm to Genentech. *Id.* ¶¶ 79-95.

b. Lost market share

Amgen's launch of Kanjinti undisputedly will reduce Genentech's market share, another form of irreparable harm. *See, e.g., Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008); *Purdue Pharma L.P. v. Boehringer*

Ingelheim GmbH, 237 F.3d 1359, 1368 (Fed. Cir. 2001). Kanjinti is a direct competitor of Herceptin, and Amgen itself forecasts that it will capture [redacted] of the trastuzumab market (which is currently all with Genentech). Ex. 29, AMGKAN02926063.

It will be difficult for Genentech to recapture market share from Amgen. As Amgen's own documents confirm, it expects that its customers will be [redacted]. *Id*. Even if Amgen were later removed from the market, Genentech is unlikely to recapture its pre-entry market share. Ex. 28, Jena Decl. ¶98. For example, Kanjinti's launch is expected to prime the marketplace for other biosimilar entrants as well as for any subsequent re-launch of Kanjinti. *Id*., ¶69. Moreover, unlike generic non-biologic drugs that a "substitutable" such that patients who were taking the generic drug can switch back to the innovator's product, the FDA has not determined that Kanjinti is "interchangeable" with Herceptin, meaning that patients who take Kanjinti cannot be switched back to Herceptin, and vice-versa. *See* 42 U.S.C. § 262(k)(4) (outlining requirements for interchangeability). Amgen's launch therefore will have irreversible consequences.

2. Genentech's irreparable harm is connected to Amgen's infringement.

Amgen's own actions confirm the nexus between its infringing inducement of the three-week-interval claims and the irreparable harm to Genentech. *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 640 (Fed. Cir. 2015) ("*Apple II*") (explaining that there must be "'some connection' between the harm alleged and the infringing acts"). As described above, two of the dosing patents were upheld as valid in IPRs. After these decisions, Amgen attempted to [redacted]. Ex. 19, 179:5-14, 179:24-180:4. This course of conduct, driven by Amgen's understanding of market demand, is overwhelming proof of nexus. *See Apple II*, 809 F.3d at 643 (market demand for infringing features and infringer's belief that infringing features were driver of sales "establishes a causal nexus").

The claimed dosing regimens account for most of the indications on the Herceptin label and are used in connection with a substantial majority of Herceptin prescriptions. Ex. 2, Tannenbaum Decl. ¶32. Amgen's own calculations confirm that this dosing regimen accounts for up to [redacted] of Herceptin prescriptions. *See* Ex. 30, AMGKAN2727080; Ex. 2, Tannenbaum Decl. ¶67. Thus, there is

unquestionably a nexus between Amgen's infringement and Genentech's irreparable harm.

C. Balance of Hardships

The balance of hardships factor "assesses the relative effect of granting or denying an injunction on the parties." *Apple II*, 809 F.3d at 645. This factor likewise favors Genentech.

If Genentech's request for an injunction pending appeal is denied, it will be "requir[ed] to compete against its own patented invention, with the resultant [irreparable] harm." *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1156 (Fed. Cir. 2011). Moreover, because Kanjinti has not entered the market, granting injunctive relief will achieve the "goal[] of the preliminary injunction analysis [of] maintain[ing] the status quo." *Kos Pharms., Inc. v. Andrx Corp.*, 369 F.3d 700, 729 (3d Cir. 2004).

Amgen, in contrast, will suffer no prejudice from an injunction. Because its product is not yet on the market, it does not face the same harms as Genentech. "[A]n alleged infringer's loss of market share and customer relationships, without more, does not rise to the level necessary to overcome the loss of exclusivity experienced by a patent owner due to infringing conduct." *Pfizer, Inc.*, 429 F.3d at 1382. And because no other trastuzumab biosimilars have launched, Amgen will not lose any ground in the marketplace from a brief injunction to maintain the

status quo. Indeed, Amgen's own projections indicate that [redacted]. Ex. 31, AMGKAN02909186 ([redacted]).

Furthermore, Genentech seeks to have this issue resolved as expeditiously as possible and is prepared to move as quickly as Amgen and this Court will allow. Genentech does not seek to obtain a *de facto* preliminary injunction by way of this appeal. Genentech has offered to post a $10 million bond to cover any potential harm to Amgen should any injunction be determined to have been inappropriate.

D. Public Interest

The last factor for the Court to consider is "where the public interest lies." In the preliminary-injunction context, this factor focuses "on whether a critical public interest would be injured by the grant of injunctive relief." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1369 (Fed. Cir. 2017). Here, the public interest is best served by "the enforcement of [Genentech's] patent rights." *Celsis In Vitro*, 664 F.3d at 931-932; (*See* Ex. 28, Jena Decl. ¶¶111-124.) As this Court has explained, "investment in drug research and development must be encouraged and protected by the exclusionary rights conveyed in valid patents." *Id.* at 931; *see also Sanofi-Synthelabo*, 470 F.3d at 1383-1384.

Without fully considering this factor, the district court noted that an injunction would deprive the public of access to non-infringing uses of Kanjinti, explaining that "'depriving the public of access to a large number of non-infringing features' weighs against granting an injunction." (Ex. 17 at 8 n.4 (quoting *Apple Inc.*, 735 F.3d at 1372-1373. But by Amgen's own estimation, [redacted] of patient use is covered by Genentech's patents. Ex. 30, AMGKAN2727080. This situation is nothing like that in *Apple*, where the non-infringing features included virtually every capability of a smartphone. *See Apple*, 735 F.3d at 1356-1358 (patents directed to appearance, multitouch screen, and "bounceback" display).

II. THE COURT SHOULD ORDER EXPEDITED BRIEFING OF THIS MOTION AND THE UNDERLYING APPEAL.

In order to minimize the harm to all parties, Genentech requests that the briefing on this motion and the underlying appeal be expedited. Genentech can be prepared to file its opening brief within seven days of the filing of this motion.

CONCLUSION

For the foregoing reasons, Genentech respectfully requests that the Court grant this motion.

Respectfully submitted,

/s/ William F. Lee

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Attorneys for Plaintiff-Appellant Genentech, Inc.

July 19, 2019

CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellant Genentech, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Genentech, Inc.

2. The names of the real party in interest represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Genentech, Inc. is a wholly-owned subsidiary of Roche Holdings Inc. Roche Holdings Inc.'s ultimate parent, Roche Holdings Ltd, is a publicly held Swiss corporation traded on the Swiss Stock Exchange. Upon information and belief, more than 10% of Roche Holdings Ltd's voting shares are held either directly or indirectly by Novartis AG, a publicly held Swiss corporation.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

WILMER CUTLER PICKERING HALE AND DORR LLP: Timothy Cook, Robert J. Gunther Jr., William F. Lee, Jason H. Liss, Mark D. McBriar, Helena Million-Perez, Kevin S. Prussia, Rana Sawaya, Nancy L. Schroeder

DURIE TANGRI LLP: Adam R. Brausa, Daralyn J. Durie, Eneda Hoxha, Eric C. Wiener

MCCARTER & ENGLISH, LLP: Alexandra M. Joyce, Michael P. Kelly, Daniel M. Silver

WILLIAMS & CONNOLLY LLP: David I. Berl, Thomas S. Fletcher, Paul B. Gaffney, Teagan J. Gregory, Kathryn S. Kayali, Charles L. McCloud, Jonathan S. Sidhu, Kyle E. Thomason

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

Genentech, Inc. v. Amgen, Inc., No. 18-cv-924-CFC (D. Del.)

Dated: July 19, 2019

/s/ William F. Lee

WILLIAM F. LEE
WILMER CUTLER PICKERING
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CERTIFICATE OF SERVICE

I hereby certify that, on this 19th day of July, 2019, I filed the foregoing Non-Confidential Plaintiff-Appellant Genentech, Inc.'s Emergency Motion for an Injunction Pending Resolution of Appeal and Motion to Expedite Briefing on Appeal with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

/s/ William F. Lee
WILLIAM F. LEE
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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 27(d) and 32(g), the undersigned hereby certifies that this motion complies with the type-volume limitation of Circuit Rule 27(d).

1. Exclusive of the accompanying documents as authorized by Fed. R. App. P. 27(a)(2)(B) and the exempted portions of the response as provided by Fed. R. App. P. 27(d)(2) and 32(f), the motion contains 5,185 words.

2. The motion has been prepared in proportionally spaced typeface using Microsoft Word 2010 in 14 point Times New Roman font as provided by Fed. R. App. P. 32(a)(5)-(6). As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

/s/ William F. Lee
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July 19, 2019

No. 2019-2156

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GENENTECH, INC., CITY OF HOPE,

Plaintiff-Appellant,

CITY OF HOPE,

Plaintiff,

v.

AMGEN INC.,

Defendant-Appellee.

On Appeal from the United States District Court,
for the District of Delaware, No. 18-cv-00924-CFC, Judge Colm F. Connolly

NON-CONFIDENTIAL DECLARATION OF ANDREW J. DANFORD IN SUPPORT OF PLAINTIFF-APPELLANT GENENTECH, INC.'S EMERGENCY MOTION FOR AN INJUNCTION PENDING RESOLUTION OF APPEAL AND MOTION TO EXPEDITE BRIEFING ON APPEAL

I, Andrew J. Danford, pursuant to 28 U.S.C. § 1746, declare as follows:

1. I am a partner at Wilmer Cutler Pickering Hale and Dorr LLP ("WilmerHale"), counsel to Plaintiff-Appellant Genentech, Inc. in the above captioned appeal. I have personal knowledge of the facts set forth below.

2. Attached hereto as Exhibit 1 is a true and correct copy of a news release titled, "Amgen And Allergan's MVASI™ (bevacizumab-awwb) And KANJINTI™ (trastuzumab-anns) Now Available In The United States," dated July 18, 2019.

3. Attached hereto as Exhibit 2 is a true and correct copy of the Expert Declaration of Susan Tannenbaum M.D. in Support of Genentech's Emergency Motions for Temporary Restraining Order and Preliminary Injunction, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 10, 2019), ECF No. 278. This exhibit is marked Confidential.

4. Attached hereto as Exhibit 3 is a true and correct copy of the Declaration of Christy Oliger in Support of Genentech's Motion for a Temporary Restraining Order and Preliminary Injunction, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 10, 2019), ECF No. 277. This exhibit is marked Confidential.

5. Attached hereto as Exhibit 4 is a true and correct copy of an excerpted version of Unites States Patent No. 6,627,196.

6. Attached hereto as Exhibit 5 is a true and correct copy of an excerpted version of Unites States Patent No. 7,371,379.

7. Attached hereto as Exhibit 6 is a true and correct copy of an excerpted version of Unites States Patent No. 10,160,811.

8. Attached hereto as Exhibit 7 is a true and correct copy of an excerpted version of the Herceptin Label, dated November 2018.

9. Attached hereto as Exhibit 8 is a true and correct copy of an excerpted version of the Final Written Decision in IPR2017-01139 for U.S. Patent No. 6,627,196, dated October 3, 2018.

10. Attached hereto as Exhibit 9 is a true and correct copy of an excerpted version of the Final Written Decision in IPR2017-00804 for U.S. Patent No. 6,627,196, dated October 3, 2018.

11. Attached hereto as Exhibit 10 is a true and correct copy of an excerpted version of the Final Written Decision in IPR2017-00805 for U.S. Patent No. 7,371,379 B2, dated October 3, 2018.

12. Attached hereto as Exhibit 11 is a true and correct copy of an excerpted version of the Final Written Decision in IPR2017-00140 for U.S. Patent No. 7,371,379 B2, dated October 3, 2018.

13. Attached hereto as Exhibit 12 is a true and correct copy of Genentech's Fed. R. Civ. P. 62(d) Motion for an Injunction Pending Appeal, or, in the Alternative, a 14-Day Injunction to Enable Genentech to Pursue an Expedited Motion for an Injunction Pending Appeal Before the Federal Circuit Pursuant to Fed. R. App. P. 8, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 19, 2019), ECF No. 302. This exhibit is marked Confidential.

14. Attached hereto as Exhibit 13 is a true and correct copy of Genentech's Opening Brief in Support of its Fed. R. Civ. P. 62(d) Motion for an Injunction Pending Appeal, or, in the Alternative, a 14-Day Injunction to Enable Genentech to Pursue an Expedited Motion for an Injunction Pending Appeal Before the Federal Circuit Pursuant to Fed. R. App. P. 8, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 19, 2019), ECF No. 303. This exhibit is marked Confidential.

15. Attached hereto as Exhibit 14 is a true and correct copy of a Letter to The Honorable Colm F. Connolly from Neal C. Belgam regarding Amgen's Request to Respond to Genentech's Filings Submitted on July 19, 2019, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 19, 2019), ECF No. 304.

16. Attached hereto as Exhibit 15 is a true and correct copy of the Order Denying Motion for Temporary Restraining Order, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 18, 2019), ECF No. 300.

17. Attached hereto as Exhibit 16 is a true and correct copy of Notice of Appeal to the Federal Circuit, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 19, 2019), ECF No. 301.

18. Attached hereto as Exhibit 17 is a true and correct copy of (Sealed) Memorandum Opinion, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-

00924-CFC (D. Del. July 18, 2019), ECF No. 299. This exhibit is marked Confidential.

19. Attached hereto as Exhibit 18 is a true and correct copy of an excerpted version of the Jennifer Kheim Deposition Transcript, dated May 1, 2019. This exhibit is marked Confidential.

20. Attached hereto as Exhibit 19 is a true and correct copy of an excerpted version of the Purvi Lad Deposition Transcript, dated May 30, 2019. This exhibit is marked Confidential.

21. Attached hereto as Exhibit 20 is a true and correct copy of an Amgen document titled, "Highlights of Prescribing Information." This exhibit is marked Confidential.

22. Attached hereto as Exhibit 21 is a true and correct copy of an Amgen document titled, "Highlights of Prescribing Information." This exhibit is marked Confidential.

23. Attached hereto as Exhibit 22 is a true and correct copy of an excerpted version of the Molly Benson Deposition Transcript, dated June 26, 2019. This exhibit is marked Confidential.

24. Attached hereto as Exhibit 23 is a true and correct copy of the June 18, 2019 discovery hearing transcript in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del.). This exhibit is marked Confidential.

25. Attached hereto as Exhibit 24 is a true and correct copy of Declaration of Robert Jacobson in Support of Amgen's Opposition to Genentech's Emergency Motion for a Temporary Restraining Order and Preliminary Injunction, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 10, 2019), ECF No. 286. This exhibit is marked Confidential.

26. Attached hereto as Exhibit 25 is a true and correct copy of Amgen's Opening Brief in Support of its May 26, 2017 Motion for a Preliminary Injunction, in *Amgen Inc. et al. v. Hospira, Inc.*, No. 1:15-cv-839-RGA (D. Del. June 5, 2017), ECF No. 230.

27. Attached hereto as Exhibit 26 is a true and correct copy of an excerpted version of Amgen's Opening Brief in Support of its Motion for an Emergency Injunction Pending Appeal, in *Amgen Inc. v. Amneal Pharms. LLC, et al.*, No. 1:16-cv-853-MSG, (D. Del. Mar. 26, 2019), ECF No. 440.

28. Attached hereto as Exhibit 27 is a true and correct copy of an excerpted version of Notice of Motion and Motion by Amgen for a Preliminary Injunction, in *Amgen Inc. et al. v. Sandoz Inc.*, No. 3:14-cv-04741-RS (N.D. Cal. Feb. 5, 2015), ECF No. 56.

29. Attached hereto as Exhibit 28 is a true and correct copy of Declaration of Anupam B. Jena, M.D., PhD.in Support of Genentech's Motion for Preliminary

Injunction, in *Genentech, Inc. and City of Hope v. Amgen*, No. 18-00924-CFC (D. Del. July 10, 2019), ECF No. 276. This exhibit is marked Confidential.

30. Attached hereto as Exhibit 29 is a true and correct copy of an excerpted version of an Amgen document titled, "2019 Long Range Scenario (2019-2028)," dated April 2019. This exhibit is marked Confidential.

31. Attached hereto as Exhibit 30 is a true and correct copy of an email chain that begins with an email from Linda Lai to Jerad Manley, dated July 30, 2015. This exhibit is marked Confidential.

32. Attached hereto as Exhibit 31 is a true and correct copy of an excerpted version of an Amgen presentation titled, "Oncology Biosimilars," dated March 2019. This exhibit is marked Confidential.

Executed on: July 19, 2019

/s/ Andrew J. Danford
Andrew J. Danford

EXHIBIT 1

NEWS RELEASES

Amgen And Allergan's MVASI™ (bevacizumab-awwb) And KANJINTI™ (trastuzumab-anns) Now Available In The United States

First Biosimilar Avastin® and Herceptin® Products to Launch in the United States

THOUSAND OAKS, Calif., July 18, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and Allergan plc (NYSE:AGN) today announced that MVASI™ (bevacizumab-awwb), a biosimilar to Avastin® (bevacizumab), and KANJINTI™ (trastuzumab-anns), a biosimilar to Herceptin® (trastuzumab), are now available in the United States (U.S.).

MVASI, the first oncology therapeutic biosimilar approved by the U.S. Food and Drug Administration (FDA), is approved for the treatment of five types of cancer: in combination with chemotherapy for metastatic colorectal cancer (mCRC); in combination with chemotherapy for non-squamous non-small cell lung cancer (NSCLC); recurrent glioblastoma; in combination with interferon-alfa for metastatic renal cell carcinoma; and in combination with chemotherapy for persistent, recurrent, or metastatic cervical cancer.

KANJINTI is FDA approved for all approved indications of Herceptin: for the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

"The introduction of biosimilars is an important step in increasing options for treating HER2-positive breast cancers, which account for about 25% of all breast cancers," said Paula Schneider, chief executive officer, Susan G. Komen Breast Cancer Foundation. "As patient advocates, we are working to ensure that patients are educated about biosimilars and understand that these FDA-approved treatments are just as effective as the original biologic drugs."

The Wholesale Acquisition Cost (WAC or "list price") of both MVASI and KANJINTI will be 15% lower than their reference products. MVASI is being made available at a WAC of $677.40 per 100 mg and $2,709.60 per 400 mg single-dose vial, 15% less than the WAC for Avastin. KANJINTI is being made available at a WAC of $3,697.26 per 420 mg multi-dose vial, 15% below the WAC of Herceptin. At launch, MVASI is priced 12% below the current Avastin Average Selling Price (ASP) and KANJINTI is priced 13% below the current Herceptin ASP. Both products will be available from both wholesalers and specialty distributors.

"Several years ago, Amgen made the strategic decision to invest in building a global biosimilars business, leveraging our nearly four decades of experience in developing and manufacturing best-in-class biologics," said Murdo Gordon, executive vice president of Global Commercial Operations at Amgen. "Following several recent launches in Europe, we are excited to be launching our first two biosimilars in the U.S., which will provide for immediate savings for Medicare patients and commercial payers. We have several more biosimilars advancing through our pipeline, even as we continue to drive innovation through novel therapies for cancer and other serious diseases."

The WAC price measure does not account for discounts and rebates and may be significantly higher than out-of-pocket cost for patients, which can vary depending on several factors. Medicare and commercial insurance, for example, will generally pay for MVASI and KANJINTI based on ASP rather than WAC. Out-of-pocket cost may also depend on and be reduced by additional factors, including eligibility for patient assistance.

Actual costs to patients and providers for MVASI and KANJINTI are anticipated to be lower than WAC as WAC does not reflect discounts or rebates. Out-of-pocket costs to patients will vary depending on insurance status and eligibility for patient assistance. MVASI and KANJINTI will be available from both wholesalers and specialty distributors.

"As the first products from our collaboration with Amgen to be launched in the U.S., MVASI and KANJINTI reinforce our ongoing dedication to providing patients with additional treatment options," said David Nicholson, chief research and development officer at Allergan. "We are excited about the progress we've made through this partnership and look forward to continued milestones together with our remaining biosimilar products."

Amgen and Allergan are committed to developing high-quality biosimilars supported by robust analytical and clinical packages. MVASI and KANJINTI were proven to be highly similar to, and to have no clinically meaningful differences in terms of safety and effectiveness from Avastin and Herceptin, respectively, based on a totality of evidence, which included comparative analytical, clinical safety and efficacy data. At the time of FDA approval, KANJINTI was the only trastuzumab biosimilar to incorporate the evaluation of a single transition in the clinical study, in which a portion of patients who began the study on Herceptin made a single transition to KANJINTI. This portion of the study demonstrated similar safety and immunogenicity in patients on KANJINTI who were previously on Herceptin.

Amgen has a total of 10 biosimilars in its portfolio, three of which have been approved in the U.S.

About MVASI™ (bevacizumab-awwb) in the U.S.
MVASI is a recombinant humanized monoclonal IgG1 antibody that binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

MVASI, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer (mCRC).

MVASI, in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab-containing regimen.

Limitations of Use: MVASI is not indicated for adjuvant treatment of colon cancer.

MVASI, in combination with carboplatin and paclitaxel, is indicated for the first line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC).

MVASI is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

MVAS, in combination with interferon-alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

MVASI, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

MVASI (bevacizumab-awwb) Professional Important Safety Information

Gastrointestinal (GI) perforation

- Serious and sometimes fatal GI perforation occurred at a higher incidence in bevacizumab-treated patients compared to patients treated with chemotherapy
- The incidence of GI perforation ranged from 0.3% to 3% across clinical studies
- Discontinue MVASI™ in patients with GI perforation

Surgery and wound healing complications

- The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients
- Withhold MVASI™ for at least 28 days prior to elective surgery. Do not administer MVASI™ for at least 28 days after surgery and until the wound is fully healed
- Discontinue in patients with wound healing complications requiring medical intervention

Hemorrhage

- Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%
- Do not administer MVASI™ to patients with serious hemorrhage or a recent history of hemoptysis (≥1/2 tsp of red blood)
- Discontinue MVASI™ in patients who develop grade 3-4 hemorrhage

Additional serious and sometimes fatal adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:

- Non-GI fistulae (<1% to 1.8%, highest in patients with cervical cancer)
- Arterial thromboembolic events (grade ≥3, 5%, highest in patients with GBM)
- Renal injury and proteinuria
  - Grade 3-4 proteinuria ranged from 0.7% to 7% in clinical studies
  - Nephrotic syndrome (<1%)

Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:

- Venous thromboembolism (grade ≥3, 11% seen in GOG-0240)
- Hypertension (grade 3-4, 5%-18%)
- Posterior reversible encephalopathy syndrome (PRES) (<0.5%)
- Congestive heart failure (CHF) (1%)

Infusion reactions with the first dose of bevacizumab occurred in <3% of patients, and severe reactions occurred in 0.2% of patients

Avoid use in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction

Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with MVASI™

Pregnancy warning

- Based on the mechanism of action and animal studies, MVASI™ may cause fetal harm when administered to pregnant women
- Advise female patients that MVASI™ may cause fetal harm, and to inform their healthcare provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with MVASI™ and for 6 months after the last dose
- Advise nursing women that breastfeeding is not recommended during treatment with MVASI™ and for 6 months following their last dose of treatment
- MVASI™ may impair fertility

Most Common Adverse Events

- Across indications, the most common adverse reactions observed in bevacizumab -treated patients at a rate of >10% were: epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Across all studies, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions

Indication-Specific Adverse Events

- In CC, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (≥2%) in 218 patients receiving bevacizumab plus chemotherapy compared to 222 patients receiving

chemotherapy alone, were abdominal pain (12% vs 10%), diarrhea (6% vs 3%), anal fistula (4% vs 0%), proctalgia (3% vs 0%), urinary tract infection (8% vs 6%), cellulitis (3% vs 0.5%), fatigue (14% vs 10%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), hypokalemia (7% vs 4%), hyponatremia (4% vs 1%), dehydration (4% vs 0.5%), neutropenia (8% vs 4%), lymphopenia (6% vs 3%), back pain (6% vs 3%), and pelvic pain (6% vs 1%)

- In mRCC, the most common grade 3-5 adverse events in AVOREN, occurring at a >2% higher incidence in bevacizumab-treated patients vs controls, were fatigue (13% vs 8%), asthenia (10% vs 7%), proteinuria (7% vs 0%), hypertension (6% vs 1%, including hypertension and hypertensive crisis), and hemorrhage (3% vs 0.3%;, including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma)
- In rGBM Study EORTC 26101, 22% of patients discontinued treatment in the bevacizumab with lomustine arm due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving bevacizumab with lomustine, the adverse reaction profile was similar to that observed in other approved indications
- In NSCLC, grade 3-5 (nonhematologic) and grade 4-5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in bevacizumab-treated patients vs controls were neutropenia (27% vs 17%), fatigue (16% vs 13%), hypertension (8% vs 0.7%), infection without neutropenia (7% vs 3%), venous thromboembolism (5% vs 3%), febrile neutropenia (5% vs 2%), pneumonitis/pulmonary infiltrates (5% vs 3%), infection with grade 3 or 4 neutropenia (4% vs 2%), hyponatremia (4% vs 1%), headache (3% vs 1%), and proteinuria (3% vs 0%)
- In first-line mCRC, the most common grade 3-4 events in Study 2107, which occurred at a ≥2% higher incidence in the bevacizumab plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)
- In second-line mCRC, the most common grade 3-5 (nonhematologic) and 4-5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the bevacizumab plus FOLFOX4 vs FOLFOX4 groups, were fatigue (19% vs 13%), diarrhea (18% vs 13%), sensory neuropathy (17% vs 9%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), hypertension (9% vs 2%), abdominal pain (8% vs 5%), hemorrhage (5% vs 1%), other neurological (5% vs 3%), ileus (4% vs 1%), and headache (3% vs 0%). These data are likely to underestimate the true adverse event rates due to the reporting mechanisms used in this study

You may report side effects to the FDA at (800) FDA-1088 or **www.fda.gov/medwatch (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=1943775537&u=http%3A%2F%2Fwww.fda.gov%2Fmedwatch&a=www.fda.gov%2Fmedwatch)**. You may also report side effects to Amgen at 1-800-772-6436.

Please see full Prescribing Information at www.Amgen.com (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=1135124236&u=http%3A%2F%2Fwww.amgen.com%2F&a=www.Amgen.com).

About KANJINTI™ (trastuzumab-anns) in the U.S.

KANJINTI is a biosimilar to Herceptin, a recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody. The active ingredient of KANJINTI is a humanized monoclonal antibody that has the same amino acid sequence, structure and function as Herceptin. KANJINTI has the same pharmaceutical dosage form and same strength after reconstitution as Herceptin.

In the U.S., KANJINTI is approved for:

Adjuvant Breast Cancer

KANJINTI is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
- As part of treatment with docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

* High-risk is defined as ER/PR positive with one of the following features: tumor size >2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

KANJINTI is indicated:

- In combination with paclitaxel for the first line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Gastric Cancer

KANJINTI is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction

adenocarcinoma, who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

KANJINTI™ U.S. Boxed WARNINGS and Important Safety Information

Boxed WARNINGS and Additional Important Safety Information

Cardiomyopathy

- **Trastuzumab products administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens**
- **Evaluate left ventricular function in all patients prior to and during treatment with KANJINTI™. Discontinue KANJINTI™ treatment in patients receiving adjuvant therapy and withhold KANJINTI™ in patients with metastatic disease for clinically significant decrease in left ventricular function**

Infusion Reactions; Pulmonary Toxicity

- **Trastuzumab products administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt KANJINTI™ infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue KANJINTI™ for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome**

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**

Cardiomyopathy

- **Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant breast cancer trial, one patient who developed CHF died of cardiomyopathy**
- Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death

- Trastuzumab products can also cause asymptomatic decline in left ventricular ejection fraction (LVEF)
- Discontinue KANJINTI™ treatment in patients receiving adjuvant breast cancer therapy and withhold KANJINTI™ in patients with metastatic disease for clinically significant decrease in left ventricular function

Cardiac Monitoring

- **Evaluate cardiac function prior to and during treatment. For adjuvant breast cancer therapy, also evaluate cardiac function after completion of KANJINTI™**
- Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Monitor frequently for decreased left ventricular function during and after KANJINTI™ treatment
- Monitor more frequently if KANJINTI™ is withheld for significant left ventricular cardiac dysfunction

Infusion Reactions

- **KANJINTI™ administration can result in serious and fatal infusion reactions**
- **Symptoms usually occur during or within 24 hours of KANJINTI™ administration**
- **Interrupt KANJINTI™ infusion for dyspnea or clinically significant hypotension**
- **Monitor patients until symptoms completely resolve**
- **Discontinue KANJINTI™ for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Strongly consider permanent discontinuation in all patients with severe infusion reactions**
- Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion include nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- Verify the pregnancy status of females of reproductive potential prior to the initiation of KANJINTI™
- Advise pregnant women and females of reproductive potential that exposure to KANJINTI™ during pregnancy or within 7 months prior to conception can result in fetal harm

- Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of KANJINTI™. Advise female patients to contact their healthcare provider with a known or suspected pregnancy
- Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for KANJINTI™ treatment and any potential adverse effects on the breastfed child from KANJINTI™ or from the underlying maternal condition

Pulmonary Toxicity

- **Trastuzumab products can result in serious and fatal pulmonary toxicity,** which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue KANJINTI™ in patients experiencing pulmonary toxicity

Exacerbation of Chemotherapy-Induced Neutropenia

- In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not

Most Common Adverse Reactions

- The most common adverse reactions associated with trastuzumab products in breast cancer were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
- The most common adverse reactions associated with trastuzumab products in metastatic gastric cancer were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

You may report side effects to the FDA at (800) FDA-1088 or **www.fda.gov/medwatch (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=1943775537&u=http%3A%2F%2Fwww.fda.gov%2Fmedwatch&a=www.fda.gov%2Fmedwatch)**. You may also report side effects to Amgen at 1-800-772-6436.

Please see full Prescribing Information, including Boxed WARNINGS, at www.Amgen.com (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=1135124236&u=http%3A%2F%2Fwww.amgen.com%2F&a=www.Amgen.com).

About the Amgen and Allergan Collaboration

In December 2011, Amgen and Allergan plc. (then Watson Pharmaceuticals, Inc.) formed a collaboration to develop and commercialize, on a worldwide basis, four oncology antibody biosimilar medicines. This collaboration reflects the shared belief that the development and commercialization of biosimilar products will not follow a pure brand or generic model and will require significant expertise, infrastructure, and investment to ensure safe, reliably supplied therapies for patients. Under the terms of the agreement, Amgen assumes primary responsibility for developing, manufacturing and initially commercializing the oncology antibody products.

About Amgen Biosimilars

Amgen is committed to building upon Amgen's experience in the development and manufacturing of innovative human therapeutics to expand Amgen's reach to patients with serious illnesses. Biosimilars will help to maintain Amgen's commitment to connect patients with vital medicines, and Amgen is well positioned to leverage its nearly four decades of experience in biotechnology to create high-quality biosimilars and reliably supply them to patients worldwide.

For more information, visit www.amgenbiosimilars.com (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=941404754&u=http%3A%2F%2Fwww.amgenbiosimilars.com%2F&a=www.amgenbiosimilars.com) and follow us on www.twitter.com/amgenbiosim (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=3813907586&u=http%3A%2F%2Fwww.twitter.com%2Famgenbiosim&a=www.twitter.com%2Famgenb

About Amgen Oncology

Amgen is searching for and finding answers to incredibly complex questions that will advance care and improve lives for cancer patients and their families. Our research drives us to understand the disease in the context of the patient's life – not just their cancer journey – so they can take control of their lives.

For the last four decades, we have been dedicated to discovering the firsts that matter in oncology and to finding ways to reduce the burden of cancer. Building on our heritage, Amgen continues to advance the largest pipeline in the Company's history, moving with great speed to advance those innovations for the patients who need them.

At Amgen, we are driven by our commitment to transform the lives of cancer patients and keep them at the center of everything we do.

For more information, follow us on www.twitter.com/amgenoncology (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=470975526&u=http%3A%2F%2Fwww.twitter.com%2Famgenoncology&a=www.twitter.com%2Famger

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com (http://www.amgen.com) and follow us on www.twitter.com/amgen (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=2528775298&u=http%3A%2F%2Fwww.twitter.com%2Famgen&a=www.twitter.com%2Famgen).

About Allergan plc

Allergan plc (NYSE: AGN), headquartered in Dublin, Ireland, is a bold, global pharmaceutical leader. Allergan is focused on developing, manufacturing and commercializing branded pharmaceutical, device, biologic, surgical and regenerative medicine products for patients around the world.

Allergan markets a portfolio of leading brands and best-in-class products primarily focused on four key therapeutic areas including central nervous system, eye care, medical aesthetics and gastroenterology.

Allergan is an industry leader in Open Science, a model of research and development, which defines our approach to identifying and developing game-changing ideas and innovation for better patient care. With this approach, Allergan has built one of the broadest development pipelines in the pharmaceutical industry.

Allergan's success is powered by our global colleagues' commitment to being Bold for Life. Together, we build bridges, power ideas, act fast and drive results for our customers and patients around the world by always doing what is right.

With commercial operations in approximately 100 countries, Allergan is committed to working with physicians, healthcare providers and patients to deliver innovative and meaningful treatments that help people around the world live longer, healthier lives every day.

For more information, visit Allergan's website at www.Allergan.com (https://c212.net/c/link/?t=0&l=en&o=2529385-1&h=3459571952&u=https%3A%2F%2Furldefense.proofpoint.com%2Fv2%2Furl%3Fu%3Dhttp-3A__www.Allergan.com%26d%3DDwMGaQ%26c%3DSexio4usKrYWFsrnxgjbcQ%26r%3D18nQDdemER

Amgen Forward-Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including its most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those Amgen projects. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for Amgen to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and Amgen expects similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints Amgen has selected. Amgen develops product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as Amgen may have believed at the time of entering into such relationship. Also, Amgen or others could identify safety, side effects or manufacturing problems with its products, including its devices, after they are on the market.

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Allergan plc Forward-Looking Statements

Statements contained in this press release that refer to future events or other non-historical facts are forward-looking statements that reflect Allergan's current perspective on existing trends and information as of the date of this release. Actual results may differ materially from Allergan's current expectations depending upon a number of factors affecting Allergan's business. These factors include, among others, the difficulty of predicting the timing or outcome of FDA approvals or actions, if any; the impact of competitive products and pricing; market acceptance of and continued demand for Allergan's products; the impact of uncertainty around timing of generic entry related to key products, including RESTASIS®, on our financial results; risks associated with divestitures, acquisitions, mergers and joint ventures; risks related to impairments; uncertainty associated with financial projections, projected cost reductions, projected debt reduction, projected synergies, restructurings, increased costs, and adverse tax consequences; difficulties or delays in manufacturing; and other risks and uncertainties detailed in Allergan's periodic public filings with the Securities and Exchange Commission, including but not

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(Redacted in Full)

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US006627196B1

(12) **United States Patent**
Baughman et al.

(10) **Patent No.: US 6,627,196 B1**
(45) **Date of Patent: Sep. 30, 2003**

(54) **DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(75) Inventors: **Sharon A. Baughman**, Ventura, CA (US); **Steven Shak**, Burlingame, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/648,067**

(22) Filed: **Aug. 25, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/213,822, filed on Jun. 23, 2000, and provisional application No. 60/151,018, filed on Aug. 27, 1999.

(51) **Int. Cl.**[7] **A61K 39/395**

(52) **U.S. Cl.** **424/138.1**; 424/131.1; 424/133.1; 424/134.1; 424/135.1; 424/136.1; 424/137.1; 424/139.1; 424/141.1; 424/142.1; 424/143.1; 424/144.1; 424/145.1; 424/146.1; 424/147.1; 424/150.1; 424/151.1; 424/152.1; 424/153.1; 424/154.1; 424/155.1; 424/156.1; 424/158.1; 424/172.1; 424/174.1

(58) **Field of Search** 424/130.1, 138.1, 424/141.1, 142.1, 152.1, 155.1, 131.1, 133.1, 134.1, 135.1, 136.1, 137.1, 139.1, 143.1, 144.1, 145.1, 146.1, 147.1, 150.1, 151.1, 153.1, 154.1, 156.1, 158.1, 172.1, 174.1

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(57) **ABSTRACT**

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with anti-ErbB2 antibody.

33 Claims, 5 Drawing Sheets

DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES

RELATED APPLICATIONS

This application is a non-provisional application filed under 37 CFR 1.53(b)(1), claiming priority under 35 USC 119(e) to provisional application No. 60/151,018, filed Aug. 27, 1999 and No. 60/213,822, filed Jun. 23, 2000, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2 or disorders expressing epidermal growth factor receptor (EGFR), comprising administering to a human or animal presenting the disorders a therapeutically effective amount of an antibody that binds ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 or expressing EGFR, where the treatment is with an anti-ErbB2 antibody administered by front loading the dose of antibody during treatment by intravenous and/or subcutaneous administration. The invention optionally includes treatment of cancer in a human patient with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent, such as, but not limited to, a taxoid. The taxoid may be, but is not limited to paclitaxel or docetaxel. The invention further includes treatment of cancer in a human patient with a combination of anti-ErbB2 antibody and a chemotherapeutic agent, such as, but not limited to, an anthracycline derivative. Optionally, treatment with a combination of anti-ErbB2 and an anthracycline derivative includes treatment with an effective amount of a cardioprotectant. The present invention further concerns infrequent dosing of anti-ErbB2 antibodies.

BACKGROUND OF THE INVENTION

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. It has been found that the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., *Science* 235:177–182 [1987]; Slamon et al., *Science* 244:707–712 [1989]).

Several lines of evidence support a direct role for ErbB2 in the pathogenesis and clinical aggressiveness of ErbB2-overexpressing tumors. The introduction of ErbB2 into non-neoplastic cells has been shown to cause their malignant transformation (Hudziak et al., *Proc. Natl. Acad. Sci. USA* 84:7159–7163 [1987]; DiFiore et al., *Science* 237:78–182 [1987]). Transgenic mice that express HER2 were found to develop mammary tumors (Guy et al., *Proc. Natl. Acad. Sci. USA* 89:10578–10582 [1992]).

Antibodies directed against human erbB2 protein products and proteins encoded by the rat equivalent of the erbB2 gene (neu) have been described. Drebin et al., *Cell* 41:695–706 (1985) refer to an IgG2a monoclonal antibody which is directed against the rat neu gene product. This antibody called 7.16.4 causes down-modulation of cell surface p185 expression on B104-1-1 cells (NIH-3T3 cells transfected with the neu proto-oncogene) a inhibits colony formation of these cells. In Drebin et al. *PNAS (USA)* 83:9129–9133 (1986), the 7.16.4 antibody was shown to

inhibit the tumorigenic growth of neu-transformed NIH-3T3 cells as well as rat neuroblastoma cells (from which the neu oncogene was initially isolated) implanted into nude mice. Drebin et al. in *Oncogene* 2:387–394 (1988) discuss the production of a panel of antibodies against the rat neu gene product. All of the antibodies were found to exert a cytostatic effect on the growth of neu-transformed cells suspended in soft agar. Antibodies of the IgM, IgG2a and IgG2b isotypes were able to mediate significant in vitro lysis of neu-transformed cells in the presence of complement, whereas none of the antibodies were able to mediate high levels of antibody-dependent cellular cytotoxicity (ADCC) of the neu-transformed cells. Drebin et al. *Oncogene* 2:273–277 (1988) report that mixtures of antibodies reactive with two distinct regions on the p185 molecule result in synergistic anti-tumor effects on neu-transformed NIH-3T3 cells implanted into nude mice. Biological effects of anti-neu antibodies are reviewed in Myers et al., *Meth. Enzym.* 198:277–290 (1991). See also WO94/22478 published Oct. 13, 1994.

Hudziak et al., *Mol. Cell. Biol.* 9(3):1165–1172 (1989) describe the generation of a panel of anti-ErbB2 antibodies which were characterized using the human breast tumor cell line SKBR3. Relative cell proliferation of the SKBR3 cells following exposure to the antibodies was determined by crystal violet staining of the monolayers after 72 hours. Using this assay, maximum inhibition was obtained with the antibody called 4D5 which inhibited cellular proliferation by 56%. Other antibodies in the panel,including 7C2 and 7F3, reduced cellular proliferation to a lesser extent in this assay. Hudziak et al. conclude that the effect of the 4D5 antibody on SKBR3 cells was cytostatic rather than cytotoxic, since SKBR3 cells resumed growth at a nearly normal rate following removal of the antibody from the medium. The antibody 4D5 was further found to sensitize p 185 -overexpressing breast tumor cell lines to the cytotoxic effects of TNF-α. See also WO89/06692 published Jul. 27, 1989. The anti-ErbB2 antibodies discussed in Hudziak et al. are further characterized in Fendly et al. *Cancer Research* 50:1550–1558 (1990); Kotts et al. *In Vitro* 26(3):59A (1990); Sarup et al. *Growth Regulation* 1:72–82 (1991); Shepard et al. *J. Clin. Immunol.* 11(3):117–127 (1991); Kumar et al. *Mol. Cell. Biol.* 11(2):979–986 (1991); Lewis et al. *Cancer Immunol. Immunother.* 37:255–263 (1993); Pietras et al. *Oncogene* 9:1829–1838 (1994); Vitetta et al. *Cancer Research* 54:5301–5309 (1994); Sliwkowski et al. *J. Biol. Chem.* 269(20): 14661–14665 (1994); Scott et al. *J. Biol. Chem.* 266:14300–5 (1991); and D'souza et al. *Proc. Natl. Acad. Sci.*91:7202–7206 (1994).

Tagliabue et al. *Int. J. Cancer* 47:933–937 (1991) describe two antibodies which were selected for their reactivity on the lung adenocarcinoma cell line (Calu-3) which overexpresses ErbB2. One of the antibodies, called MGR3, was found to internalize, induce phosphorylation of ErbB2, and inhibit tumor cell growth in vitro.

McKenzie et al. *Oncogene* 4:543–548 (1989) generated a panel of anti-ErbB2 antibodies with varying epitope specificities, including the antibody designated TA1. This TA1 antibody was found to induce accelerated endocytosis of ErbB2 (see Maier et al. *Cancer Res.* 51:5361–5369 [1991]). Bacus et al. *Molecular Carcinogenesis* 3:350–362 (1990) reported that the TA1 antibody induced maturation of the breast cancer cell lines AU-565 (which overexpresses the erbB2 gene) and MCF-7 (which does not). Inhibition of growth and acquisition of a mature phenotype in these cells was found to be associated with reduced levels of ErbB2 receptor at the cell surface and transient increased levels in the cytoplasm.

administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week. Preferably the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment. The front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment. The subcutaneous delivery of maintenance doses according to the invention has the advantage of being convenient for the patient and health care professionals, reducing time and costs for drug treatment. Preferably, the initial dose (or the last dose within an initial dose series) is separated in time from the first subsequent dose by 4 weeks or less, preferably 3 weeks or less, more preferably 3 weeks or less, most preferably 1 week or less.

In an embodiment of the invention, the initial dose of anti-ErbB2 is 6 mg/kg, 8 mg/kg, or 12 mg/kg delivered by intravenous or subcutaneous administration, such as intravenous infusion or subcutaneous bolus injection. The subsequent maintenance doses are 2 mg/kg delivered once per week by intravenous infusion, intravenous bolus injection, subcutaneous infusion, or subcutaneous bolus injection. The choice of delivery method for the initial and maintenance doses is made according to the ability of the animal or human patient to tolerate introduction of the antibody into the body. Where the antibody is well-tolerated, the time of infusion may be reduced. The choice of delivery method as disclosed for this embodiment applies to all drug delivery regimens contemplated according to the invention.

In another embodiment, the invention includes an initial dose of 12 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of 6 mg/kg once per 3 weeks.

In still another embodiment, the invention includes an initial dose of 8 mg/kg anti-ErbB2 antibody, followed by 6 mg/kg once per 3 weeks.

In yet another embodiment, the invention includes an initial dose of 8 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of8 mg/kg once per week or 8 mg/kg once every 2 to 3 weeks.

In another embodiment, the invention includes initial doses of at least 1 mg/kg, preferably 4 mg/kg, anti-ErbB2 antibody on each of days 1, 2 and 3, followed by subsequent maintenance doses of 6 mg/kg once per 3 weeks.

In another embodiment, the invention includes an initial dose of 4 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of 2 mg/kg twice per week, wherein the maintenance doses are separated by 3 days.

In still another embodiment, the invention includes a cycle of dosing in which delivery of anti-ErbB2 antibody is 2–3 times per week for 3 weeks. In one embodiment of the invention, each dose is approximately 25 mg/kg or less for a human patient, preferably approximately 10 mg/kg or less. This 3 week cycle is preferably repeated as necessary to achieve suppression of disease symptoms.

In another embodiment, the invention includes a cycle of dosing in which delivery of anti-ErbB2 antibody is daily for 5 days. According to the invention, the cycle is preferably repeated as necessary to achieve suppression of disease symptoms.

The disorder preferably is a benign or malignant tumor characterized by the overexpression of the ErbB2 receptor, e.g. a cancer, such as, breast cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer. The method of the invention may further comprise administration of a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin. The chemotherapeutic agent preferably is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative.

Preferred anti-ErbB2 antibodies bind the extracellular domain of the ErbB2 receptor, and preferably bind o the epitope 4D5 or 3H4 within the ErbB2 extracellular domain sequence. More preferably, the antibody is the antibody 4D5, most preferably in a humanized form. Other preferred ErbB2-binding antibodies include, but are not limited to, antibodies 7C2, 7F3, and 2C4, preferably in a humanized form.

The method of the present invention is particularly suitable for the treatment of breast or ovarian cancer, characterized by the overexpression of the ErbB2 receptor.

The present application also provides a method of therapy involving infrequent dosing of an anti-ErbB2 antibody. In particular, the invention provides a method for the treatment of cancer (e.g. cancer characterized by overexpression of the ErbB2 receptor) in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by at least one subsequent dose of the antibody, wherein the first dose and subsequent dose are separated from each other in time by at least about two weeks (e.g. from about two weeks to about two months), and optionally at least about three weeks (e.g. from about three weeks to about six weeks). For instance, the antibody may be administered about every three weeks, about two to about 20 times, e.g. about six times. The first dose and subsequent dose may each be from about 2 mg/kg to about 16 mg/kg; e.g. from about 4 mg/kg to about 12 mg/kg; and optionally from about 6 mg/kg to about 12 mg/kg. Generally, two or more subsequent doses (e.g. from about two to about ten subsequent doses) of the antibody are administered to the patient, and those subsequent doses are preferably separated from each other in time by at least about two weeks (e.g. from about two weeks to about two months), and optionally at least about three weeks (e.g. from about three weeks to about six weeks). The two or more subsequent doses may each be from about 2 mg/kg to about 16 mg/kg; or from about 4 mg/kg to about 12 mg/kg; or from about 6 mg/kg to about 12 mg/kg. The invention additionally provides an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB2 antibody, and a package insert containing instructions to administer the antibody according to such methods.

The presently described dosing protocols may be applied to other anti-ErbB antibodies such as anti-epidermal growth factor receptor (EGFR), anti-ErbB3 and anti-ErbB4 antibodies. Thus, the invention provides a method for the treatment of cancer in a human patient, comprising administering an effective amount of an anti-ErbB antibody to the human patient, the method comprising administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB antibody; and administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose. Alternatively, or additionally, the invention pertains to a method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB antibody followed by at least one subsequent dose of the antibody, wherein the first dose and subsequent dose are separated from each other in time by at least about two

weeks. The invention additionally provides an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB antibody, and a package insert containing instructions to administer the antibody according to such methods.

In another aspect, the invention concerns an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB2 antibody, optionally a label on or associated with the container that indicates that the composition can be used for treating a condition characterized by overexpression of ErbB2 receptor, and a package insert containing instructions to avoid the use of anthracycline-type chemotherapeutics in combination with the composition. According to the invention, the package insert further includes instructions to administer the anti-ErbB2 antibody at an initial dose of 5 mg/kg followed by the same or smaller subsequent dose or doses. In another embodiment of the invention, the package insert further includes instructions to administer the anti-ErbB2 antibody subcutaneously for at least one of the doses, preferably for all of the subsequent doses following the initial dose, most preferably for all doses.

In a further aspect, the invention provides a method of treating ErbB2 expressing cancer in a human patient comprising administering to the patient effective amounts of an anti-ErbB2 antibody and a chemotherapeutic agent. In one embodiment of the invention, the chemotherapeutic agent is a taxoid including, but not limited to, paclitaxel and docetaxel. In another embodiment, the chemotherapeutic agent is an anthracyline derivative including, but not limited to, doxorubicin or epirubicin. In still another embodiment of the invention, treatment with an anti-ErbB2 antibody and an anthracycline derivative further includes administration of a cardioprotectant to the patient. In still another embodiment, an anthracycline derivative is not administered to the patient with the anti-ErbB2 antibody. One or more additional chemotherapeutic agents may also be administered to the patient. The cancer is preferably characterized by overexpression of ErbB2.

The invention further provides an article of manufacture comprising a container, a composition within the container comprising an anti-ErbB2 antibody and a package insert instructing the user of the composition to administer the anti-ErbB2 antibody composition and a chemotherapeutic agent to a patient. In another embodiment, the chemotherapeutic agent is other than an anthracycline, and is preferably a taxoid, such as TAXOL®. In still another embodiment, the chemotherapeutic agent is an anthracycline, including but not limited to, doxorubicin or epirubicin. In yet another embodiment, the chemotherapeutic agent is an anthracycline and the package insert further instructs the user to administer a cardioprotectant.

The methods and compositions of the invention comprise an anti-ErbB2 antibody and include a humanized anti-ErbB2 antibody. Thus, the invention further pertains to a composition comprising an antibody that binds ErbB2 and the use of the antibody for treating ErbB2 expressing cancer, e.g., ErbB2 overexpressing cancer, in a human. The invention also pertains to the use of the antibody for treating EGFR expressing cancer. Preferably the antibody is a monoclonal antibody 4D5, e.g., humanized 4D5 (and preferably huMAb4D5–8 (HERCEPTIN® anti-ErbB2 antibody); or monoclonal antibody 2C4, e.g., humanized 2C4. The antibody may be an intact antibody (e.g., an intact IgG, antibody) or an antibody fragment (e.g., a Fab, $F(ab')_2$, diabody, and the like). The variable light chain and variable heavy chain regions of humanized anti-ErbB2 antibody 2C4 are shown in FIGS. **5**A and **5**B.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows epitope-mapping of the extracellular domain of ErbB2 as determined by truncation mutant analysis and site-directed mutagenesis (Nakamura et al. *J. of Virology* 67 (10):6179–6191 [October 1993]; Renz et *J. Cell Biol.* 125(6):1395–1406 [June 1994]). The anti-proliferative MAbs 4D5 and 3H4 b bind adjacent to the transmembrane domain. The various ErbB2-ECD truncations or point mutations were prepared from cDNA using polymerase chain reaction technology. The ErbB2 mutants were expressed as gD fusion proteins in a mammalian expression plasmid. This expression plasmid uses the cytomegalovirus promoter/enhancer with SV40 termination and polyadenylation signals located downstream of the inserted cDNA. Plasmid DNA was transfected into 293S cells. One day following transfection, the cells were metabolically labeled overnight in methionine and cysteine-free, low glucose DMEM containing 1% dialyzed fetal bovine serum and 25 μCi each of ^{35}S methionine and ^{35}S cysteine. Supernatants were harvested either the ErbB2 MAbs or control antibodies were added to the supernatant and incubated 2–4 hours at 4° C. The complexes were precipitated, applied to a 10–20% Tricine SDS gradient gel and electrophoresed at 100 V. The gel was electroblotted onto a membrane and analyzed by autoradiography. SEQ ID NOs:8 and 9 depict the 3H4 and 4D5 epitopes, respectively.

FIG. **2** depicts with underlining the amino acid sequence of Domain 1 of ErbB2 (SEQ ID NO: 1). Bold amino acids indicate the location of the epitope recognized by MAbs 7C2 and 7F3 as determined by deletion mapping, i.e. the "7C2/7F3 epitope" (SEQ ID NO:2).

FIG. **3** is a graph of anti-ErbB2 antibody (HERCEPTIN®) trough serum concentration (μg/ml, mean ±SE, dark circles) by week from week 2 through week 36 for ErbB2 overexpressing patients treated with HERCEPTIN® anti-ErbB2 antibody at 4 mg/kg initial dose, followed by 2 mg/kg weekly. The number of patients at each time point is represented by "n" (white squares).

FIG. **4**A is a linear plot of tumor volume changes over time in mice treated with HERCEPTIN® anti-ErbB2 antibody. FIG. **4**B is a semi-logarithmic plot of the same data as in FIG. **4**A such that the variation in tumor volume for the treated animals is observed more readily.

FIGS. **5**A and **5**B depict alignments of the amino acid sequences of the variable light (V_L)(FIG. **5**A) and variable heavy (V_H) (FIG. **5**B) domains of murine monoclonal antibody 2C4 (SEQ ID Nos. 10 and 11, respectively); V_L and V_H domains of humanized Fab version 574 (SEQ ID Nos. 12 and 13, respectively), and human V_L and V_H consensus frameworks (hum κl, light kappa subgroup I; humIII, heavy subgroup III) (SEQ ID Nos. 14 and 15, respectively). Asterisks identify differences between humanized Fab version 574 and murine monoclonal antibody 2C4 or between humanized Fab version 574 and the human framework. Complementarity Determining Regions (CDRs) are in brackets. Humanized Fab version 574, with the changes ArgH71Val, AspH73Arg and IleH69Leu, appears to have binding restored to that of the original chimeric 2C4 Fab fragment. Additional FR and/or CDR residues, such as L2, L54, L55, L56, H35 and/or H48, may be modified (e.g. substituted as follows-IleL2Thr; ArgL54Leu; TyrL55Glu; ThrL56Ser; AspH35Ser; and ValH48Ile) in order to further refine or enhance binding of the humanized antibody. Alternatively, or additionally, the humanized antibody may be affinity matured in order to further improve or refine its affinity and/or other biological activities.

the subsequent doses are separated in time from each other by at least two weeks.

2. The method of claim **1**, wherein the initial dose is at least approximately 6 mg/kg.

3. The method of claim **2**, wherein the initial dose is at least approximately 8 mg/kg.

4. The method of claim **3**, wherein the initial dose is at least approximately 12 mg/kg.

5. The method of claim **1**, wherein the subsequent doses are separated in time from each other by at least three weeks.

6. The method of claim **1**, wherein the initial dose is administered by intravenous injection, and wherein at least one subsequent dose is administered by subcutaneous injection.

7. The method of claim **1**, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered by a method selected from the group consisting of intravenous injection and subcutaneous injection.

8. The method of claim **1**, wherein the initial dose and at least one subsequent dose are administered by subcutaneous injection.

9. The method of claim **1**, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg.

10. The method of claim **9**, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks.

11. The method of claim **10**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

12. The method of claim **10**, wherein the initial dose is approximately 12 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

13. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 8 mg/kg.

14. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, wherein at least one subsequent dose is 8 mg/kg, and wherein administration of the initial dose and subsequent doses are separated in time by at least 2 weeks.

15. The method of claim **14**, wherein the initial dose and subsequent doses are separated in time by at least 3 weeks.

16. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

administering to the patient an initial dose of the antibody, wherein the initial dose is a plurality of doses, wherein each of the plurality of initial doses is at least approximately 1 mg/kg and is administered on at least 3 consecutive days, and administering to the patient at least 1 subsequent dose of the antibody, wherein at least one subsequent dose is at least approximately 6 mg/kg, and wherein administration of the last initial dose and the first subsequent and additional subsequent doses are separated in time by at least 3 weeks.

17. The method of claim **1**, wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

18. The method of claim **17**, wherein said cancer is breast cancer.

19. The method of claim **18**, wherein said cancer is metastatic breast carcinoma.

20. The method of claim **1**, wherein said antibody binds to the extracellular domain of the ErbB2 receptor.

21. The method of claim **20**, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

22. The method of claim **21**, wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.

23. The method of claim **1**, wherein efficacy is measured by determining the time to disease progression or the response rate.

24. A method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses of the antibody, wherein the subsequent doses are separated in time from each other by at least two weeks.

25. The method of claim **24**, wherein the first dose and a first subsequent dose are separated from each other in time by at least about three weeks.

26. The method of claim **24**, wherein the first dose and subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

27. The method of claim **26**, wherein the first dose and subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

28. The method of claim **27**, wherein the first dose and subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

29. The method of claim **24**, wherein from about two to about ten subsequent doses of the antibody are administered to the patient.

30. The method of claim **24**, wherein the subsequent doses are separated in time from each other by at least about three weeks.

31. The method of claim **24**, wherein the two or more subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

32. The method of claim **24**, wherein the two or more subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

33. The method of claim **24**, wherein the two or more subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

* * * * *

EXHIBIT 5

US007371379B2

(12) **United States Patent**
Baughman et al.

(10) **Patent No.: US 7,371,379 B2**
(45) **Date of Patent: May 13, 2008**

(54) **DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

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(21) Appl. No.: **10/600,152**

(22) Filed: **Jun. 20, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(60) Provisional application No. 60/213,822, filed on Jun. 23, 2000, provisional application No. 60/151,018, filed on Aug. 27, 1999.

(51) **Int. Cl.**
A61K 39/395 (2006.01)

(52) **U.S. Cl.** **424/138.1**; 424/130.1; 424/133.1; 424/141.1; 424/142.1; 424/143.1; 424/155.1; 424/156.1; 424/174.1

(58) **Field of Classification Search** 424/130.1, 424/133.1, 138.1, 141.1, 142.1, 143.1, 155.1, 424/156.1, 174.1
See application file for complete search history.

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(57) **ABSTRACT**

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with anti-ErbB2 antibody.

40 Claims, 5 Drawing Sheets

-continued

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Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
             35                  40                  45

Glu Trp Val Ala Val Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr
             50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
             65                  70                  75

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
             80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu
             95                 100                 105

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            110                 115
```

The invention claimed is:

1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and

administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and

further comprising administering an effective amount of a chemotherapeutic agent to the patient.

2. The method of claim **1**, wherein the initial dose is at least approximately 6 mg/kg.

3. The method of claim **2**, wherein the initial dose is at least approximately 8 mg/kg.

4. The method of claim **3**, wherein the initial dose is at least approximately 12 mg/kg.

5. The method of claim **1**, wherein the subsequent doses are separated in time from each other by at least three weeks.

6. The method of claim **1**, wherein the initial dose is administered by intravenous injection, and wherein at least one subsequent dose is administered by subcutaneous injection.

7. The method of claim **1**, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered by a method selected from the group consisting of intravenous injection and subcutaneous injection.

8. The method of claim **1**, wherein the initial dose and at least one subsequent dose are administered by subcutaneous injection.

9. The method of claim **1**, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg.

10. The method of claim **9**, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks.

11. The method of claim **10**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

12. The method of claim **10**, wherein the initial dose is approximately 12 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

13. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 8 mg/kg.

14. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, wherein at least one subsequent dose is 8 mg/kg, and wherein administration of the initial dose and subsequent doses are separated in time by at least 2 weeks.

15. The method of claim **14**, wherein the initial dose and subsequent doses are separated in time by at least 3 weeks.

16. The method of claim **1**, wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

17. The method of claim **16**, wherein said cancer is breast cancer.

EXHIBIT 6

US010160811B2

(12) United States Patent

Baughman et al.

(10) Patent No.: US 10,160,811 B2
(45) Date of Patent: *Dec. 25, 2018

(54) **TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(71) Applicant: **GENENTECH, INC.**, South San Francisco, CA (US)

(72) Inventors: **Sharon A. Baughman**, Ventura, CA (US); **Steven Shak**, Burlingame, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 843 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/073,659**

(22) Filed: **Nov. 6, 2013**

(65) **Prior Publication Data**

US 2014/0079692 A1 Mar. 20, 2014

Related U.S. Application Data

(60) Continuation of application No. 13/415,271, filed on Mar. 8, 2012, now abandoned, which is a continuation of application No. 13/167,599, filed on Jun. 23, 2011, now abandoned, which is a continuation of application No. 11/443,943, filed on May 31, 2006, now abandoned, which is a division of application No. 10/600,152, filed on Jun. 20, 2003, now Pat. No. 7,371,379, which is a division of application No. 09/648,067, filed on Aug. 25, 2000, now Pat. No. 6,627,196.

(60) Provisional application No. 60/213,822, filed on Jun. 23, 2000, provisional application No. 60/151,018, filed on Aug. 27, 1999.

(51) **Int. Cl.**

C07K 16/30	(2006.01)
A61K 39/395	(2006.01)
C07K 16/32	(2006.01)
A61K 45/06	(2006.01)
A61K 31/337	(2006.01)
A61K 39/00	(2006.01)
A61K 38/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/30*** (2013.01); ***A61K 31/337*** (2013.01); ***A61K 39/395*** (2013.01); ***A61K 39/39558*** (2013.01); ***A61K 45/06*** (2013.01); ***C07K 16/32*** (2013.01); *A61K 38/00* (2013.01); *A61K 2039/505* (2013.01); *A61K 2039/54* (2013.01); *A61K 2039/545* (2013.01)

(58) **Field of Classification Search**

CPC A61K 47/48384

See application file for complete search history.

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Primary Examiner — Ilia I Ouspenski

(74) *Attorney, Agent, or Firm* — Diane L. Marschang; Ginger R. Dreger

(57) **ABSTRACT**

The present invention concerns dosages for treatment of human cancer patients with an anti-Epidermal Growth Factor Receptor (EGFR) antibody.

12 Claims, 5 Drawing Sheets

Specification includes a Sequence Listing.

needle). At least one active agent in the composition is an anti-ErbB2 antibody. The label on, or associated with, the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes. In addition, the article of manufacture may comprise a package inserts with instructions for use, including, e.g., a warning that the composition is not to be used in combination with anthacycline-type chemotherapeutic agent, e.g. doxorubicin or epirubicin.

Deposit of Materials

The following hybridoma cell lines have been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md., USA (ATCC):

Antibody Designation	ATCC No.	Deposit Date
7C2	ATCC HB-12215	Oct. 17, 1996
7F3	ATCC HB-12216	Oct. 17, 1996
4D5	ATCC CRL 10463	May 24, 1990
2C4	ATCC HB-12697	Apr. 8, 1999

Further details of the invention are illustrated by the following non-limiting Examples.

EXAMPLES

Example 1: Preparation and Efficacy of HERCEPTIN® Anti-ErbB2 Antibody

Materials and Methods

Anti-ErbB2 Monoclonal Antibody

The anti-ErbB2 $IgG_1\kappa$ murine monoclonal antibody 4D5, specific for the extracellular domain of ErbB2, was produced as described in Fendly et al., *Cancer Research* 5o:1550-1558 (1990) and WO89/06692. Briefly, NIH 3T3/HER2-3_{400} cells (expressing approximately 1×10^5 ErbB2 molecules/cell) produced as described in Hudziak, et al., *Proc. Natl. Acad. Sci. (USA)* 84:7159 (1987) were harvested with phosphate buffered saline (PBS) containing 25 mM EDTA and used to immunize BALB/c mice. The mice were given injections i.p. of 10^7 cells in 0.5 ml PBS on weeks, 0, 2, 5 and 7. The mice with antisera that immunoprecipitated ^{32}P-labeled ErbB2 were given i.p. injections of a wheat germ agglutinin-Sepharose (WGA) purified ErbB2 membrane extract on weeks 9 and 13. This was followed by an i.v. injection of 0.1 ml of the ErbB2 preparation and the splenocytes were fused with mouse myeloma line X63-Ag8.653. Hybridoma supernatants were screened for ErbB2-binding by ELISA and radioimmunoprecipitation. MOPC-21 (IgG1), (Cappell, Durham, N.C.), was used as an isotype-matched control.

The treatment was performed with a humanized version of the murine 4D5 antibody (HERCEPTIN® anti-ErbB2 antibody). The humanized antibody was engineered by inserting the complementarity determining regions of the murine 4D5 antibody into the framework of a consensus human immunoglobulin IgG_1 (IgG_1) (Carter et al., *Proc. Natl. Acad. Sci. USA* 89:4285-4289 [1992]). The resulting humanized anti-ErbB2 monoclonal antibody has high affinity for $p185^{HER2}$ (Dillohiation constant [K_d]=0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody-dependent cellular cytotoxicity (ADCC), and has been found clinically active, as a single agent, in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior therapy. HERCEPTIN® anti-ErbB2 antibody is produced by a genetically engineered Chinese Hamster Ovary (CHO) cell line, grown in large scale, that secretes the antibody into the culture medium. The antibody is purified from the CHO culture media using standard chromatographic and filtration methods. Each lot of antibody used in this study was assayed to verify identity, purity, and potency, as well as to meet Food and Drug Administration requirements for sterility and safety.

Eligibility Criteria

Patients had to fulfill all of the following criteria to be eligible for study admission:

- Metastatic breast cancer
- Overexpression of the ErbB2 (HER2) oncogene (2+ to 3+ as determined by immunohistochemistry or fluorescence in situ hybridization (FISH). [Tumor expression of ErbB2 can be determined by immunohistochemical analysis, as previously described (Slamon et al., [1987] and [1989], supra), of a set of thin sections prepared from the patient's paraffin-archived tumor blocks. The primary detecting antibody used is murine 4D5 MAb, which has the same CDRs as the humanized antibody used for the treatment. Tumors are considered to overexpress ErbB2 if at least 25% of tumor cells exhibit characteristic membrane staining for $p185^{HER2}$].
- Bidimensionally measurable disease (including lytic bone lesions) by radiographic means, physical examination, or photographs

Measurable disease was defined as any mass reproducibly measurable in two perpendicular diameters by physical examination, X-ray (plain films), computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, or photographs.

Osteoblastic metastases, pleural effusions, or ascites were not considered to be measurable. Measurable lesions must be at least 1 cm in greatest dimension. Enumeration of evaluable sites of metastatic disease and number of lesions in an evaluable site (e.g. lung) had to be recorded on the appropriate Case Report Form (CRF). If a large number of pulmonary or hepatic lesions were present, the six largest lesions per site were followed.

- The ability to understand and willingness to sign a written informed consent form
- Women ≤18 years
- Suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening laboratory assessments of hematologic, renal, hepatic, and metabolic functions.

Exclusion Criteria

Patients with any of the following were excluded from study entry:

- Prior cytotoxic chemotherapy for metastatic breast cancer
- Patients may have received prior hormonal therapy (e.g. tamoxifen) for metastatic disease or cytotoxic therapy in the adjuvant setting.
- Concomitant malignancy that has not been curatively treated
- A performance status of <60% on the Karnofsky scale
- Pregnant or nursing women; women of childbearing potential, unless using effective contraception as determined by the investigator

-continued

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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Arg Val Gly Tyr Ser Leu Tyr Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

The invention claimed is:

1. A method for the treatment of a human patient diagnosed with breast cancer characterized by 2+ or 3+ overexpression of ErbB2 receptor as determined by immunohistochemistry or fluorescence in situ hybridization (FISH), comprising the steps of administering to the patient an initial dose of 8 mg/kg of anti-ErbB2 huMAb 4D5-8 antibody; and administering to the patient a plurality of subsequent doses of 6 mg/kg of the antibody, wherein all doses are separated in time from each other by three weeks.

2. The method of claim **1**, further comprising administering an effective amount of a chemotherapeutic agent.

3. The method of claim **2**, wherein said chemotherapeutic agent is a taxoid.

4. The method of claim **3**, wherein said taxoid is paclitaxel or docetaxel.

5. The method of claim **4** wherein said taxoid is paclitaxel.

6. The method of claim **1**, wherein said antibody is administered by intravenous injection.

7. A method for the treatment of a human patient diagnosed with breast cancer characterized by 2+ or 3+ overexpression of ErbB2 receptor as determined by immunohistochemistry or fluorescence in situ hybridization (FISH), the method comprising: administering intravenously to the patient an initial dose of 8 mg/kg of anti-ErbB2 huMAb 4D5-8 antibody; and administering intravenously to the patient a plurality of subsequent 6 mg/kg doses of the antibody, wherein the initial dose is separated in time from the first subsequent dose by three weeks, and the subsequent doses are separated from each other in time by three weeks.

8. The method of claim **7**, wherein the intravenous administration is an intravenous infusion.

9. The method of claim **8**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 10 μg/mL.

10. The method of claim **8**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 20 μg/mL.

11. The method of claim **7**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 10 μg/mL.

12. The method of claim **7**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 20 μg/mL.

* * * * *

EXHIBIT 7

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Herceptin safely and effectively. See full prescribing information for Herceptin.

HERCEPTIN® (trastuzumab) for injection, for intravenous use
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: Herceptin can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------INDICATIONS AND USAGE----------

Herceptin is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution
- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

- Most common adverse reactions (≥5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Herceptin (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)]*.

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.**
- **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer

- Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer

- Administer Herceptin at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[See Boxed Warning, Warnings and Precautions (5.2)]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

Cardiomyopathy

[See Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%.

Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not ado-trastuzumab emtansine.

420 mg Multiple-dose vial

Reconstitution

Reconstitute each 420 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab that delivers 20 mL (420 mg trastuzumab). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized powder of Herceptin, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

Table 4 (cont'd)

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

Table 5

Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1% between Arms) and Higher Incidence in Herceptin Arm

Body System/Adverse Event	Herceptin + FC (N = 294) N (%)		FC (N = 290) N (%)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	15 (5)	—	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤ 1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections and Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal and Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

EXHIBIT 8

Trials@uspto.gov
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Paper No. 68
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01139
Patent 6,627,196 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Granting Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Reasonable Expectation of Success

Claims 24, 25, 29, and 30 do not recite either the first or any subsequent dosage amount of trastuzumab. In addition, claims 26 and 31 recite the first dose and subsequent doses "are each from about 2 mg/kg to about 16 mg/kg." As explained above, we find an ordinary artisan would have been motivated to modify the dosing frequency of trastuzumab as claimed. In addition, both Slamon and Herceptin Product Label teach the loading dose of 4 mg/kg and the maintenance doses of 2 mg/kg. Ex. 1005, 5; Ex. 1008, 2. Even so, we find Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable. This is because Petitioner's analysis of these claims hinges on the same argument of 8 mg/kg loading dose and 6 mg/kg maintenance doses Petitioner asserts in the other claims. For example, the substantive analysis of claim 24, in its entirety, appears in a single paragraph:

> As discussed above with respect to claim 1, it would have been obvious to administer trastuzumab on an every-three-week regimen as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses. *See also* Ex. 1003 at ¶¶ 89–112. This regimen would have satisfied each and every element of claim 24 of the '196 patent, and therefore claim 24 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶¶ 89–112, 115–118.

Pet. 43.

For claim 1, Petitioner analyzes the reasonable expectation of success with respect to efficacy based on an 8 mg/kg loading dose and 6 mg/kg maintenance doses. Pet. 32–38, 42. Because Petitioner has not met its burden to show that an ordinary artisan would have been motivated to modify the dosage amount in the first instance, its reasonable-expectation-

of-success arguments, premised upon efficacy associated with administering those modified dosage amounts over the every-three-week dosing frequency, also fail.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable.

Motions to Exclude

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2004, 2039, 2041, 2061, 2062, and 2067. Paper 51. Patent Owner does not oppose. Paper 55.

Petitioner's Motion to Exclude is granted.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1100, 1102, 1105, 1107, 1111, 1121, 1124, 1125, 1126, 1128, and 1130, as well as paragraphs 22, 29, 35–37, 44, 53–58, and 60–73 of Exhibit 1123, i.e., the Reply Declaration of Dr. Ratain. Paper 53. Patent Owner filed an Identification of Improper New Reply Materials, challenging the same exhibits. Paper 52.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[8] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a

[8] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

EXHIBIT 9

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00804[1]
Patent 6,627,196 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01958 has been joined with IPR2017-00804

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 67. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 68.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

EXHIBIT 10

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00805[1]
Patent 7,371,379 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01959 has been joined with IPR2017-00805.

I. INTRODUCTION

Hospira, Inc. ("Hospira") filed a Petition (Paper 1, "Pet."), requesting institution of an *inter partes* review of claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of U.S. Patent No. 7,371,379 B2 (Ex. 1001, "the '379 patent"). Genentech, Inc. timely filed a Patent Owner Preliminary Response (Paper 6, "Prelim. Resp."). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Hospira would prevail in challenging claims 1–3, 5, 7, 9–11, 16–28, and 30–40 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on July 27, 2017, as to those claims of the '379 patent. Paper 13 ("Institution Decision" or "Inst. Dec."). Following our institution based on Hospira's Petition, Samsung Bioepis Co., Ltd. ("Samsung") filed a substantially identical Petition challenging the same claims of the '379 patent and requested joinder in this proceeding, which we granted. Paper 40. Thus, Hospira and Samsung together are the "Petitioners" in this proceeding.

Patent Owner filed its Response to the Petition (Paper 42, "PO Resp.") and Petitioners filed a Reply to Patent Owner's Response (Paper 56, "Reply"). Patent Owner filed a Motion to Exclude certain evidence (Paper 64), to which Petitioners filed an Opposition (Paper 69) and Patent Owner filed a Reply in support thereof (Paper 73). Patent Owner also filed a Motion for Observations on Cross-Examination of Petitioners' Reply Declarants (Drs. Allan Lipton and William Jusko) (Paper 65) to which Petitioners filed a Response (Paper 70). Additionally, pursuant to our authorization, Patent Owner filed an Identification of Improper New Reply Materials (Paper 68), to which Petitioners filed a Response (Paper 72) and

Patent Owner filed a Reply (Paper 74). An oral hearing was held on May 8, 2018. The transcript of the hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioners have *not* demonstrated by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent are unpatentable.

A. Related Proceedings

As a related matter, Petitioners and Patent Owner identify a concurrently-filed petition for *inter partes* review (IPR2017-00804) for a related patent, U.S. Patent 6,627,196 ("the '196 patent"). *See* Pet. 2. We issue our Final Written Decision in IPR2017-00804 concurrently with this decision. Additionally, also concurrently with this Decision, we issue Final Written Decisions in two other *inter partes* review proceedings concerning the '196 and '379 patents brought by another petitioner. IPR2017-01139; IPR2017-001140.

The parties also identify litigation matters pending in the U.S. District Courts for the Northern District of California and the District of Delaware and on appeal before the Federal Circuit Court of Appeals concerning the '379 and '196 patents, as well as foreign proceedings concerning counterparts to these patents, as related matters. Paper 81; Paper 82.

B. The '379 Patent (Ex. 1001)

The '379 patent issued on May 13, 2008, with Sharon A. Baughman and Steven Shak as the listed co-inventors. Ex. 1001, (45), (75). The '379 patent claims priority as the divisional of an application filed August 25,

2000, as well as to provisional applications filed June 23, 2000, and August 27, 1999. *Id.* at (22), (60). The parties have not disputed the claimed priority date for the '379 patent.

The '379 patent relates generally to dosages for the treatment of disorders characterized by the overexpression of ErbB2 (also known as HER2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR). *Id.* at 1:15–25, 44–50. The overexpression of ErbB2 has been associated with breast cancer. *Id.* As noted in the '379 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (alternatively referred to as "rhuMab HER2," "trastuzumab," or by its tradename "Herceptin")[2] had been clinically tested and approved for patients with ErbB2-overexpressing metastatic breast cancers who received prior anti-cancer therapy. *Id.* at 3:59–65. The recommended initial "loading dose" for trastuzumab was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:66–4:3.

The invention described in the '379 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies, followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:26–31.

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[2] For consistency's sake, we will refer to the antibody at issue in this proceeding as trastuzumab unless we are directly quoting one of its alternative names from another document.

The method of treatment, according to the invention described in the patent, "involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:51–55. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:65–5:2. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 µg/ml and does not fall below 0.01 µg/ml during treatment." *Id.* at 5:4–9. The patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:9–12. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:31–34. Additionally, the patent states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and second dose are separated by at least two weeks, and optionally at least about three weeks. *Id.* at 6:23–36.

The '379 patent describes embodiments in which the initial dose of trastuzumab is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 µg/ml during the treatment period. *Id.* at 5:19–43, 45:19–45. The treatment regimen according to the invention may further

comprise administration of chemotherapy along with trastuzumab. *Id.* at 6:6–10, 7:26–32, 46:28–58. Of particular relevance, the '379 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:60–48:32. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [μ]g/ml, in the range (10–20 [μ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 47:1–5. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '379 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:28–31.

C. Illustrative Claim

Petitioners challenge claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 Patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:
> administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Ex. 1001, 57:33–46.

D. The Asserted Ground of Unpatentability

Petitioners challenge the patentability of the claims of the '379 Patent based on the following ground:

References	**Basis**	**Claims challenged**
Herceptin label,[3] Baselga '96,[4] Pegram '98,[5] and the knowledge of a person of ordinary skill in the art	§ 103(a)	1–3, 5, 7, 9–11, 16–28, and 30–40

Petitioners further rely upon the declarations of Allan Lipton, M.D. (Ex. 1002; Ex. 1056) and William Jusko, Ph.D. (Ex. 1003; Ex. 1057). Patent Owner relies upon the declarations of George Grass, Ph.D. (Ex. 2039) and Karen Gelmon, M.D. (Ex. 2040).

II. ANALYSIS

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim

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[3] Genentech, Inc, Herceptin® Trastuzumab, Sept. 1998 (hereinafter "Herceptin Label" (Ex. 1008).

[4] Jose Baselga, *Phase ll Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 JOURNAL OF CLINICAL ONCOLOGY 737–744 (1996) (hereinafter "Baselga '96") (Ex. 1013).

[5] Mark D. Pegram, *Phase ll Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185^{HER21neu} Monoclonal Antibody Plus Cisplatin in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16 JOURNAL OF CLINICAL ONCOLOGY 2659–71 (1998) (hereinafter "Pegram '98") (Ex. 1014).

terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioners propose a construction for "ErbB2 receptor." *See* Pet. 24. Patent Owner does not propose any terms to be construed in its post-institution Response. We find that no explicit construction of any claim term is necessary to decide the issues presented in this case. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Level of Skill in the Art

Petitioners contend that a person of ordinary skill in the art for the '379 patent would be a "team" that includes both (1) a clinical or medical oncologist specializing in breast cancer with several years of experience in breast cancer research or clinical trials, and (2) a person with a Ph.D. in pharmaceutical sciences or a closely related field with an emphasis in pharmacokinetics with three years of relevant experience in protein based

drug kinetics. Pet. 23–24 (citing Exs. 1002 ¶ 14; 1003 ¶ 15; 1006 ¶ 32). Patent Owner does not address the requisite level of skill in its Response.

Because it is otherwise undisputed and consistent with the evidence of record, we adopt Petitioners' proposed definition of a person of ordinary skill in the art ("POSITA" or "skilled artisan") for purposes of our analysis. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Patentability Analysis

1. Content of the Prior Art

Petitioners rely upon, *inter alia*, the following prior art teachings to support their challenge.

a. Herceptin Label (Ex. 1008)

As recognized in the '379 patent, trastuzumab was already FDA-approved and commercially sold in the U.S. by 1998 under the tradename Herceptin. Ex. 1001, 3:59–4:3. The Herceptin label teaches:

> The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly

> dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL.

Ex. 1008, 1.

The Herceptin label also teaches that "[i]n studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days . . . was observed," and "[b]etween week 16 and 32, Trastuzumab serum concentration reached a steady state with a mean trough and peak concentrations of approximately 79 [mg]/mL and 123 [mg]/mL, respectively. *Id.* The label further describes clinical studies in which metastatic breast cancer patients with certain levels of HER2 overexpression were administered chemotherapy either alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses at 2 mg/kg. *Id.* The chemotherapy in these clinical studies (e.g., paclitaxel) was administered every 3 weeks (21 days). *Id.*

b. Baselga '96 (Ex. 1013)

Baselga '96 reports the results of a phase II clinical trial in which patients with ErbB2-overexpressing metastatic breast cancer were treated with trastuzumab. Ex. 1013, 737. The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 738. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to the results reported in Baselga '96, "[m]ore than 90% of the examined population (41 patients) had rhuMAb HER2 trough levels above the targeted 10 μg/mL level. *Id.* at 739. Moreover, the treatment "was remarkably well tolerated." *Id.* "Toxicity [from rhuMAb HER2] was

minimal," and no immune response against the antibody was detected. *Id.* at 737. Out of the 768 times trastuzumab was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 739. Baselga '96 also teaches that in preclinical studies (both *in vitro* and in xenografts), trastuzumab "markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 743.

c. Pegram '98 (Ex. 1014)

Pegram '98 reports the results of a phase II clinical trial using a combination of trastuzumab plus cisplatin. Ex. 1014, 2659. Pegram '98 states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 µg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 2660. Pegram '98 also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that trastuzumab did not increase toxicity. *Id.* at 2668.

2. Obviousness Based on the Herceptin Label, Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art of the Prior Art

Petitioners have provided a claim-by-claim explanation for the basis of their contention that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 are obvious over the Herceptin label in view of Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art. Pet. 29–54.

In general terms, the challenged claims are directed to a dosing regimen for the treatment of cancer in which trastuzumab is administered at an initial dose, followed by administration of the antibody at subsequent

doses that are the same or less than the initial dose and separated in time by at least about two weeks. Independent claim 1 specifies an initial dose of approximately 5 mg/kg, while certain dependent claims specify higher initial doses of 6 mg/kg, 8 mg/kg, or 12 mg/kg (e.g., cls. 2, 3, 9), whereas other dependent claims specify that the subsequent doses are separated in time by at least three weeks (e.g., cls. 5, 10). Our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

Petitioners rely upon the teaching in the Herceptin label that trastuzumab doses of up to 500 mg had been successfully administered to patients. Pet. 31 (citing Ex. 1008, 1). Based on a patient weight range of 55–85 kg, Petitioners calculate that the weight-based dose for the 500 mg absolute dose taught by the Herceptin label ranges from 5.88–9.09 mg/kg. *Id.* at 31–32 (citing Ex. 1002 ¶¶ 55–57; Ex. 1003 ¶ 45; Ex. 1026, 3; Ex. 1027, 334 (Table 7-2)). Petitioners further rely upon the Herceptin label's teaching that trastuzumab doses should be "front-loaded" with a higher initial dose of 4 mg/kg followed by a lower weekly maintenance dose of 2 mg/kg. *Id.* at 33. Additionally, Petitioners rely upon the teaching in the Herceptin label describing the administration of trastuzumab in combination with chemotherapeutic agents, and that these chemotherapeutic agents are administered once every three weeks to patients. *Id.* at 35–36, 43–44. Petitioners further rely upon Baselga '96 and Pegram '98 insofar as they confirm that the weekly dosing regimen encompassed by the Herceptin label was successfully administered to patients in phase II clinical trials, and that

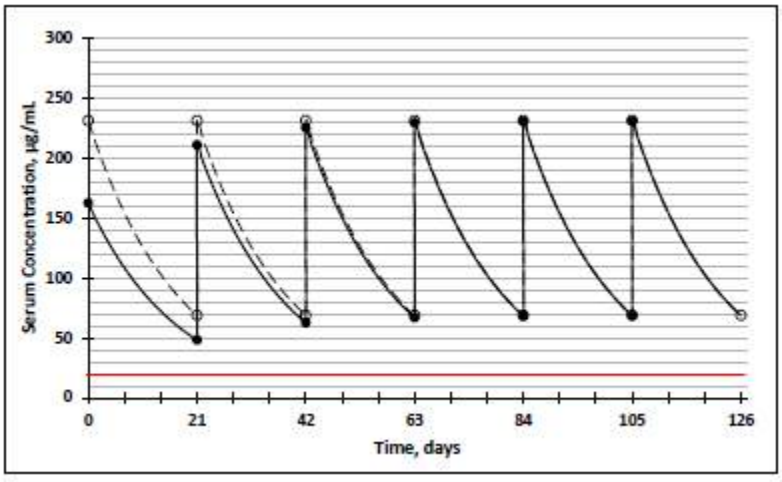
the skilled artisan would have been aware of a target trough serum concentration of 10–20 µg/mL for trastuzumab. Pet. 33, 37.

Petitioners acknowledge that the Herceptin label, along with Baselga '96 and Pegram '98, teach only a *weekly* dosing regimen, but assert that the skilled artisan would nonetheless have been motivated to decrease the frequency of trastuzumab administration to once every three weeks for several reasons. *Id.* at 34–42. First, Petitioners contend that "a skilled artisan would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—, and to improve patient compliance and quality of life." *Id.* at 34. Second, Petitioners contend that the skilled artisan would have been motivated to apply a tri-weekly (i.e., once every three weeks) regimen for the antibody in order to align with the dosing schedules of the chemotherapy so that a patient would only have to make one trip to the clinic to receive both doses. *Id.* at 36. In support, Petitioners rely upon their oncology expert, Dr. Lipton, who attests that each trip to the clinic to receive even a single infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43.

Petitioners further contend that the skilled artisan would confidently decrease the frequency of injections and use a tri-weekly dosing regimen in view of trastuzumab's known pharmacokinetic properties. *Id.* at 36. Petitioners contend that arriving at the tri-weekly dosing schedule was merely a matter of "routine calculation and optimization" of the therapy outlined in the Herceptin label. *Id.* at 37. In this regard, Petitioners rely upon data from the Herceptin label and Dr. Jusko's opinions to assert that it

would have been a matter of routine calculation for a skilled artisan to determine that a tri-weekly 500 mg trastuzumab dosing regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 µg/mL reported in the prior art. *Id.* at 37–39 (citing Ex. 1003 ¶¶ 46–47, 49–51, 56–58, 62).

Specifically, Dr. Jusko, assuming a "one-compartment" model to approximate drug concentration over time, calculated the initial minimum drug concentration three weeks after first administering a 500 mg antibody dose to a 70 kg patient to be 48.3 µg/mL and the steady-state trough concentration after multiple doses to be 68.7 µg/mL. Ex. 1003 ¶¶ 46–58. Additionally, assuming linear (first-order) kinetics, Dr. Jusko calculated that a 712 mg loading dose followed by 500 mg tri-weekly maintenance doses could be administered to patients while keeping serum drug concentrations within acceptable levels. *Id.* ¶¶ 59–66. Dr. Jusko provides the following graph depicting expected trastuzumab concentrations over time for a 70 kg patient administered 500 mg of trastuzumab every three weeks, with or without an initial 712 mg loading dose (broken and solid lines, respectively):



Ex. 1003 ¶ 62 (Fig. 2). As shown in the figure above, when administering either calculated dosing regimen, Dr. Jusko concludes that the trastuzumab serum concentration would have been expected to stay well above the target minimum trough concentration of 10–20 μg/ml (with 20 μg/ml shown in red). *Id.* ¶ 63.

As noted by Petitioners, Dr. Jusko made three assumptions in performing his calculations: (1) that trastuzumab exhibits non-exponential kinetics; (2) that the initial concentration (C_0) can be estimated by multiplying the dose by the volume of distribution and average mass of a patient; and (3) that the kinetics of trastuzumab remain constant with multiple-dosing. Pet. 42 (citing Ex. 1003 ¶¶ 69–71; Ex. 1028, 91; Ex. 1029, 77).

The two main issues argued in this proceeding are: (a) whether there would have been a motivation to extend the weekly dosing interval taught in the prior art to a tri-weekly dosing interval based on concerns about patient convenience and quality of life, and (b) whether there would have been a reasonable expectation of success in implementing such a dosing regimen based on Dr. Jusko's pharmacokinetic analysis. It is Petitioners' burden to demonstrate both "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (internal citations omitted). As they are distinct legal requirements for obviousness, we address motivation and reasonable expectation of success separately in our analysis. For the reasons explained below, while skilled artisans may have

been motivated to extend the dosing interval, we find that they would not have had a reasonable expectation of success in doing so based on the prior art. Thus, we determine that Petitioners have not shown that the challenged claims are unpatentable for obviousness.

a. Motivation

As discussed above, Petitioners' primary arguments on motivation for extending the dosing interval of trastuzumab from the weekly administration taught in the prior art to tri-weekly is based on a desire to improve patient "convenience," "compliance," "efficiency," and "quality of life." Pet. 34. In its Response, Patent Owner contends these "patient-related" factors would not have served as a reason to extend the dosing interval because the primary focus for skilled artisans in developing a treatment regimen for HER2-positive breast cancer would have been on efficacy. PO Resp. 28–36. Moreover, instead of extending trastuzumab's dosing interval to a tri-weekly schedule, Patent Owner asserts that skilled artisans were actually increasing the frequency of the chemotherapy (paclitaxel) administration in numerous clinical trials so that both drugs could be administered on a weekly schedule. *Id.* at 31–32. Patent Owner also argues that this is not simply a case of selecting an optimal doses from known range of doses in the prior art since the only dosing interval disclosed was weekly. *Id.* at 26. Patent Owner notes that "at the time of the invention, developing an antibody dosing regimen for clinical use was described as a "complicated task" and such drugs "defy easy quantitative description and prediction." *Id.* at 26 (citing Ex. 2004, 11; Ex. 1022, 3:109).

We find that the skilled artisan would have been motivated to extend the dosing interval for the simple (yet compelling) reasons that doing so

would have been more cost-effective and less burdensome for the patient undergoing such treatment, which required in-person visits to the clinic for each antibody infusion. As previously recognized by the Federal Circuit, "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014). Patent Owner seeks to limit this statement in *Hoffman-La Roche* to the specific issue addressed in that case, which was whether once-monthly administration of bisphosphonate ibandronate to treat osteoporosis would have been obvious. PO Resp. 38–39. Patent Owner contends that, unlike the facts of *Hoffman-La Roche*, the claimed treatment regimen at issue in this proceeding involves a "first-in-class" therapeutic (i.e., trastuzumab was the only antibody approved at the time for the treatment of "solid" tumors), a fatal disease condition (breast cancer), and a completely different set of prior art. *Id.* at 39. Patent Owner argues that "[c]onvenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer." *Id.* at 39. We do not read *Hoffman-La Roche* to stand for a *per se* rule that it would always have been obvious to extend the dosing interval in order to address patient compliance concerns regardless of the particular medical condition or drug at issue. Nonetheless, based on the specific facts of this case, we find that skilled artisans would have been similarly motivated to administer trastuzumab less frequently to treat breast cancer patients.

In support of this finding, we take into account the real-world experiences of the parties' oncology experts, Dr. Lipton (Petitioner's expert) and Dr. Gelmon (Patent Owner's expert), who are both physicians with

extensive experience treating breast cancer patients in clinical settings. Ex. 1002 ¶¶ 4–10; Ex. 2040 ¶¶ 2–5. Dr. Lipton attests that each trip to his clinic to receive even a relatively short infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43. Indeed, some of his patients have had to travel up to one hundred miles each direction to receive treatment at the clinic. *Id.* ¶ 39. As such, we are not persuaded by Dr. Gelmon's contention that efficacy would have taken precedence over convenience as the focus of cancer treatment in the 1990s. Ex. 2040 ¶¶ 30–34. Of course, maintaining efficacy and safety would have been a paramount concern for the skilled artisan seeking to improve upon the weekly dosing regimen that was previously FDA-approved, but that does not mean improving convenience and quality of life for the patient would not have also been motivating concerns. By 1999, efficacy and safety had already been demonstrated for weekly trastuzumab administration as set forth in the Herceptin label. Ex. 1008. Notably, Dr. Gelmon admitted during her deposition that "before 1999 it was known that providing a drug less frequently might provide benefits to certain patients in terms of convenience, cost and quality of life as long as efficacy and safety were shown." Ex. 1058, 328:24-329:7. Indeed, these same concerns factored into Dr. Gelmon's own clinical study involving tri-weekly trastuzumab administration, which took place within months of the '379 patent priority date. *Id.* at 73:19–75:16.[6]

[6] While the publication of Dr. Gelmon's tri-weekly study does not qualify as prior art, we find the fact that she initiated the study so close to the priority date undermines the credibility of her testimony that skilled artisans

Contrary to Patent Owner's arguments, the prior art need not have expressly articulated or suggested patient convenience or quality of life concerns as the motivation to extend the dosing interval. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). Nonetheless, the motivation set forth by Dr. Lipton is supported by his citation to prior art articles indicating that quality of life issues for cancer patients have long been a concern to physicians. Ex. 1002 ¶ 44 (citing Coates, et al., *Quality of Life in Oncology Practice: Prognostic Value of EORTC QLQ-C30 Scores in Patients with Advanced Malignanc*y, 33(7) EUROPEAN JOURNAL OF CANCER 1025–30 (1997) (Ex. 1019); Aaronson, et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology*, 85(5) J. NAT'L CANCER INSTITUTE 365–76 (1993) (Ex. 1020); Ferrell, *Quality of Life in Breast Cancer*, 4(6) CANCER PRACTICE 331–40 (1996) (Ex. 1021)).

Additionally, we find that the skilled artisan would have been motivated to match trastuzumab and chemotherapy dosing. As indicated in

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would not have considered extending the dosing interval at the time. In their Reply, however, Petitioners identify additional post-filing evidence supporting their contention that skilled artisans were motivated by "patient-related factors" to investigate tri-weekly dosing of trastuzumab. Reply 14–15. Insofar as these additional references do not qualify as prior art themselves, nor do they purport to recount what was publicly known in the prior art, we decline to give them any weight in our analysis.

the Herceptin label, patients were often prescribed chemotherapy, such as paclitaxel or anthracycline, in combination with trastuzumab. Ex. 1008, 1. The Herceptin label indicates that both paclitaxel and anthracycline were administered once every three weeks (21 days). *Id.* In addition to convenience for the patient, Dr. Lipton notes that "it is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once." Ex. 1002 ¶ 66. Patent Owner acknowledges that researchers at the time had explored the possibility of administering paclitaxel to match weekly trastuzumab administration. PO Resp. 9; Ex. 2040 ¶¶ 38, 57; *see, e.g.*, M Fornier, *Weekly (W) Herceptin (H) + 1 Hour Taxol (T): Phase II Study in HER2 Overexpressing (H2+) and Non-Overexpressing (H2-) Metastatic Breast Cancer (MBC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 482) (1999) (Ex. 2029). But, at the time, paclitaxel was FDA-approved for only tri-weekly treatment. Ex. 1058, 180:22–181:1. Regardless, the fact that skilled artisans were considering matching the antibody and chemotherapy treatments on a weekly basis does not mean that they would also not have considered matching the treatments on a tri-weekly basis. Obviousness does not require the claimed regimen to be the only or best choice, nor may a patentee defeat obviousness simply by identifying another alternative. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case 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.").

Patent Owner also contends that skilled artisans would not have had a reason to select a 500 mg maintenance dose or 712 mg loading dose, as

calculated by Dr. Jusko. PO Resp. 24–27. We are unpersuaded by these arguments because the Herceptin label expressly teaches that a 500 mg dose was considered safe and tolerable, at least when administered on a weekly basis. Dr. Jusko explained that the 500 mg dose level, and associated 12-day half-life, would have been the obvious starting point "because that was the highest reported tolerable weekly dose level with the longest half-life that would give the POSITA the best chance of achieving the minimum serum trough concentrations to establish efficacy at three weeks." Ex. 1057 ¶ 34. Dr. Jusko further notes that "[i]t would have made no sense to choose a lower dose level, as the result of any such simulation would not have been indicative of the feasibility of three-week dosing—a negative result would merely necessitate simulating at the higher dose level, i.e., 500 mg." *Id.* Furthermore, while the 712 mg loading dose is not expressly disclosed in the prior art (Ex. 1003 ¶¶ 59–63), Patent Owner's experts Dr. Grass and Dr. Gelmon do not dispute Dr. Jusko's calculation of this amount, which is based on equations set forth in a basic pharmacokinetics textbook. Ex. 1002 ¶ 72; *see* Rowland, *et al.*, CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS (3rd ed. 1995) (vol. 1), at 88 (Ex. 1022) ("Rowland").[7]

[7] Patent Owner also argues that the pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing interval of trastuzumab. PO Resp. 40–43. We find that the skilled artisan would have been motivated to extend the dosing interval regardless of the pharmacokinetic data set forth in the prior art. But, as discussed below, we find that trastuzumab's non-linear kinetics would not have provided the skilled artisan with a reasonable expectation of success with such an extended dosing interval.

Accordingly, we find that skilled artisans would have been motivated to extend the dosing interval of trastuzumab to once every three weeks, with a 712 mg loading dose followed by 500 mg maintenance doses.

b. Reasonable Expectation of Success

Having found the requisite motivation to arrive at the claimed dosing regimen, we next turn to whether there would have had a reasonable expectation of success with such a treatment regimen. Based on our consideration of the record evidence, we find that Petitioners have not met their burden of establishing a reasonable expectation of success.

In evaluating reasonable expectation of success, we must "consider the appropriate scope of the patent's claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965–66 (Fed. Cir. 2014). Here, the claims of the '379 patent are directed to a "method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an *effective* amount of an anti-ErbB2 antibody to the human patient." Ex. 1001, 57:33–36 (emphasis added). Petitioners and Patent Owner both focus their arguments and evidence on whether the skilled artisan would have reasonably expected that trastuzumab plasma concentrations would be maintained above 10–20 μg/mL, which the prior art identifies as the minimum serum trough concentration required for efficacy. In view of the claim scope, we agree that this is an appropriate definition of "success" for purposes of our analysis.

Petitioners contend that the skilled artisan would have extended the dosing interval based on Dr. Jusko's pharmacokinetic analysis as set forth above. Patent Owner disagrees that this type of mathematical analysis would have provided the requisite reasonable expectation of success for the

claimed dosing regimen. In particular, Patent Owner criticizes Dr. Jusko's application of linear pharmacokinetics to predict serum trough concentration insofar as the prior art taught that trastuzumab had demonstrated non-linear (dose-dependent) kinetics. PO Resp. 45–48. As noted by Patent Owner, "[f]or drugs with non-linear kinetics, pharmacokinetic parameters such as half-life do not remain constant but change as a function of the concentration of the drug in the plasma." *Id.* at 46 (citing Ex. 1022, 3:109; Ex. 2008, 123; Ex. 2038 ¶¶ 22–25, 27, 34–36). According to Patent Owner, there is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective, and thus a clinical oncologist would not have confidently used three-week dosing based on Dr. Jusko's pharmacokinetic analysis. *Id.* at 55–57.

As part of our evaluation, we take into account the relative novelty of using antibodies for the treatment of cancer as of the August 27, 1999 priority date. Herceptin had been approved by the FDA for weekly administration in September 1998, less than a year before, was the first antibody approved to target "solid tumors," and the first approved to treat any form of breast cancer. Ex. 1008; Ex. 2003, 388; Ex. 2038, 33:8–17; Ex. 2040 ¶ 23.[8] Petitioners have not pointed to any prior art reference discussing the feasibility or viability of a tri-weekly antibody dosing regimen.

[8] Prior to August 1999, the FDA had approved only one other antibody for treating cancer—Patent Owner's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. Ex. 2003, 388. We find no evidence of record indicating that rituximab had been approved or successfully tested for anything longer than weekly dosing.

While Dr. Jusko's calculations are based on "textbook" equations that were known in the prior art, the actual pharmacokinetic analysis set forth in his declaration for determining the serum trough concentration associated with a tri-weekly dosing regimen of trastuzumab was not found in any prior art reference. Thus, we find Dr. Jusko's analysis to be largely based on impermissible hindsight. *KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Petitioners contend that Dr. Jusko applied the same model that Patent Owner and its collaborators did in the prior art. Reply 17. In particular, Petitioners rely upon Baselga '96's statement that "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." Ex. 1013, 738. However, Baselga '96 did not mention a tri-weekly schedule, and instead determined that a regimen in which patients received an initial dose of 250 mg trastuzumab followed by 100 mg weekly doses was the "optimal dose and schedule." *Id.* Petitioners also speculate that the Herceptin label's reporting of only a single half-life for each dosage level "suggest[s] use of a one-compartment model." Reply 17; Ex. 1003 ¶ 34. But the Herceptin label does not explicitly indicate that a one-compartment model was used to model the weekly dosing regimen discussed therein. In any event, the pharmacokinetics discussed in the Herceptin label were based on actual clinical trials rather than just mathematical predictions. Ex. 1008, 1 ("The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease."). Baselga '96 and the Herceptin label both specifically recognize that trastuzumab has "dose dependent pharmacokinetics." Ex. 1008, 1;

Ex. 1013, 738. The very pharmacokinetics textbook relied upon by Dr. Jusko notes that "dose-dependent and time-dependent kinetic behaviors defy easy quantitative description and prediction." Ex. 1022, vol. 3, 395.

We recognize that Pegram'98 states that Phase I clinical "studies showed that the pharmacokinetics of rhuMAb HER2 were predictable." Ex. 1014, 2660. But as explained by Patent Owner's pharmacokinetic expert Dr. Grass, "[a] skilled artisan would understand 'predictable' in this context to mean that administration of the same dose with the same dosing schedule would likely yield the same serum concentrations if given to a similar patient population." Ex. 2039 ¶ 54. It does not suggest predictability across different dosing intervals. Insofar as the pharmacokinetics discussed in the prior art were only based on studies of weekly administration of lower trastuzumab doses, we do not find that the references support Petitioners' conclusion that the same "one-compartment" model could also be used to reasonably predict the expected serum concentrations for tri-weekly administration using higher doses of the antibody.

The evidence shows that the prior art did not contain sufficient data from which the skilled artisan could reliably predict the plasma concentration for trastuzumab over a three-week dosing interval using a one-compartment model. In this regard, we credit the testimony of Dr. Grass. Dr. Grass explains that one potential source of non-linear kinetics for trastuzumab was the presence of "shed antigens" in the patient's serum, which are extra-cellular domain HER2 receptors (ECD^{HER2}) "shed" from the tumor source that circulate in the patient's blood stream. Ex. 2039 ¶¶ 56, 71, 72. We are unpersuaded by Dr. Jusko's opinion that the effect of shed antigens on half-life and serum trough levels would not have been of

concern to the skilled artisan because it was "only shown to be significant in the small percentage of patients for which shed antigen reached 'high levels,' *i.e.*, greater than about 0.5 µg/mL." Ex. 1057 ¶ 46 (citing Ex. 1013 and Ex. 1014).

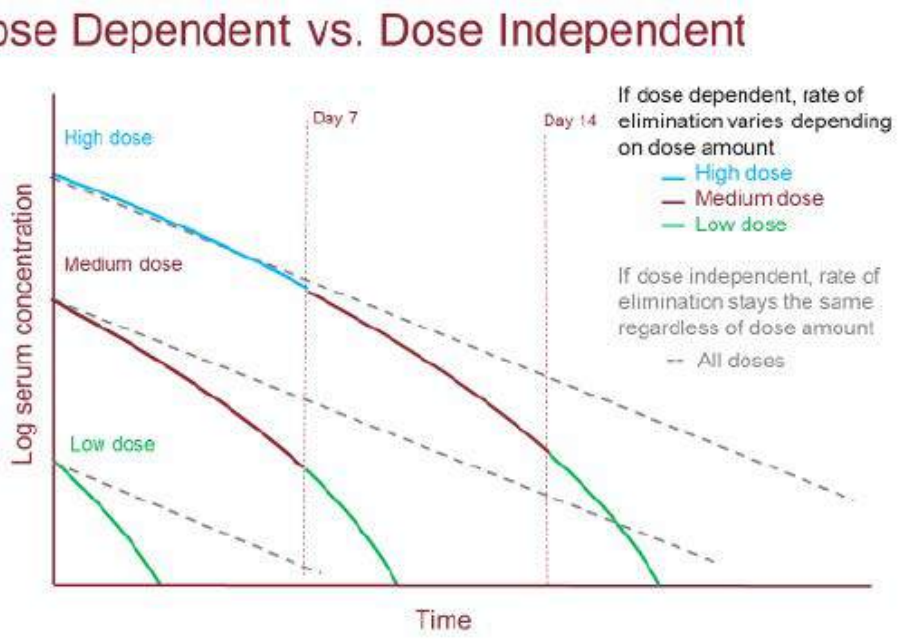
Petitioners' own prior art references highlight the uncertainty caused by the presence of shed antigens on the pharmacokinetics of trastuzumab. For instance, the Herceptin label notes that "64% of patients (287/447) had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL)," and that "[p]atients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations." Ex. 1008, 1. Baselga '96 likewise teaches that "[t]he rhuMAb HER2 serum $t_{1/2}$ was found to be dependent on the presence of circulating ECD^{HER2} released from the tumor into the serum." Ex. 1013, 739. In fact, for those patients with high levels of shed antigen, Baselga '96 teaches that serum levels of the antibody were "suboptimal," and that "the trough levels of rhuMAb HER2 were consistently below detectable levels throughout the treatment course and until disease progression." *Id.* at 739–740 (Fig. 1B). Pegram '98 notes "there was an inverse relationship between rhuMAb HER2 serum half-life and serum shed HER2 ECD of 0.5 µg/mL or greater." Ex. 1014, 2665. Pegram '98 further indicates that "patients with any measurable shed [antigen] serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations (18.7 v. 43.6 µg/mL; $P = .0001$) across all time points (n = 443 observations; Fig. 1)." Notably, this prior art data appears to show that patients with *any* detectable shed antigen levels (i.e., 64% of patients as set forth in the Herceptin label) had a mean antibody trough level that was close to the 10–

20 µg/mL threshold for efficacy.[9] As such, we find that skilled artisan would have been concerned that the effect of shed antigens— not taken into account by Dr. Jusko's analysis—could indeed significantly affect serum trough concentrations for tri-weekly administration of trastuzumab.

Contrary to Dr. Jusko's assumptions, Dr. Grass attests that "applying a constant value for half-life over a three-week period, based on the one-week data reported in the prior art, to a dose-dependent drug like trastuzumab could overestimate trough serum concentration levels" because it "fail[s] to account for the nonlinear increase in elimination and corresponding decrease in the half-life that would be expected to occur as serum concentration declines." Ex. 2039 ¶ 25. Dr. Grass also contends that the actual rates of elimination for such a drug would be unpredictable without collecting sufficient data, such as by conducting a "washout study" where serum concentration is collected over several half-lives following a single administration of the drug, but notes that there is no prior art reference for trastuzumab that describes such data. *Id.* ¶ 24.

To illustrate this point, Dr. Grass provides the following graph showing differences that can potentially exist between dose-independent drugs (which exhibit linear kinetics) and dose-dependent drugs (which exhibit non-linear kinetics):

[9] Although Dr. Gelmon testified that later (post-filing) studies showed that shed antigens were not in fact a concern for efficacy of Herceptin, and that dosage is not adjusted based on shed antigen levels today, our analysis is based on what was known in the prior art. Ex. 1058, 62:20–65:6.



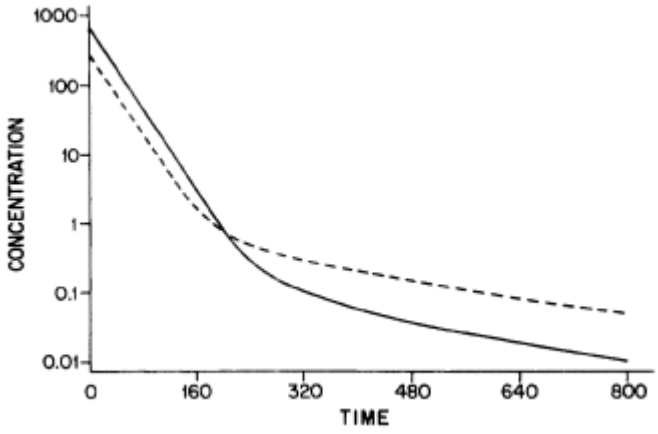
Id. ¶ 23. As shown by the solid lines in the graph above, which correspond to different dosage amounts of a dose-dependent drug, elimination increases (i.e., half-life decreases) as the drug concentration changes over time. Petitioners criticize this graph as being "made up" by Dr. Grass, as it was not derived from any particular data set forth in the prior art. Reply 20 (citing Ex. 1059, 116:16–21). Patent Owner, however, points to post-filing data concerning the anti-cancer agent indisulam as a "real-world example" of a dose-dependent drug that can behave this way, showing how assuming a constant half-life could greatly overestimate the predicted serum concentration over a longer interval. PO Resp. 49–50; Ex. 2039 ¶ 26; Anthe S. Zandvliet et al., *Saturable Binding of Indisulam to Plasma Proteins and Distribution to Human Erythrocytes*, 34 DRUG METABOLISM & DISPOSITION 1041 (2006) (Ex. 2052) ("Zandvliet"). While we recognize that Zandvliet does not qualify as prior art, and concerns a "small molecule" rather than an antibody, we find that it demonstrates at least one example in which assuming linear kinetics could result in an overestimation of trough serum

concentrations for a dose-dependent drug. From the perspective of a skilled artisan as of the August 27, 1999 priority date, we find nothing in the record to suggest that a similar overestimation would not have been a concern for tri-weekly trastuzumab administration.

With its Reply, Petitioners present additional evidence and arguments as to why Dr. Jusko's initial assumptions and analysis were reasonable. In particular, Petitioners contend that Dr. Jusko's analysis would, at worst, have underestimated, not overestimated, serum trough concentrations. Reply 18–23. In support of this contention, Petitioners cite King, APPLICATIONS AND ENGINEERING OF MONOCLONAL ANTIBODIES (1998) (Ex. 1029) ("King '98") as teaching that antibodies follow a common profile associated with "receptor-mediated" (or "target-mediated") drug disposition, with a quick initial clearance and short half-life ($t_{1/2}\alpha$), followed by slower clearance and a longer half-life ($t_{1/2}\beta$). While King '98 includes a table that identifies several antibodies known at the time to have a shorter $t_{1/2}\alpha$ followed by a longer $t_{1/2}\beta$, it *only* reports a $t_{1/2}\beta$ of 199 ± 120 hours for trastuzumab (citing Baselga '96), and Petitioners do not point to any other evidence suggesting a $t_{1/2}\alpha$ for trastuzumab. *See* Ex. 1029, 70 (Table 2.7). Furthermore, King '98 recognizes that the presence of circulating shed antigens could reduce antibody half-life in some cases, and that "[t]he pharmacokinetics of human IgG are unusual in that the half-life varies with concentration." *Id.* at 68, 70. As such, we find that King '98 does not show that Dr. Jusko's linear assumptions would have underestimated serum trough concentrations for trastuzumab.

In further support, Petitioners point to the following graph from Levy, *Pharmacologic target-mediated drug disposition*, 56(3) Clinical

Pharmacology & Therapeutics 248–52 (1994) ("Levy") as demonstrating this type of profile:

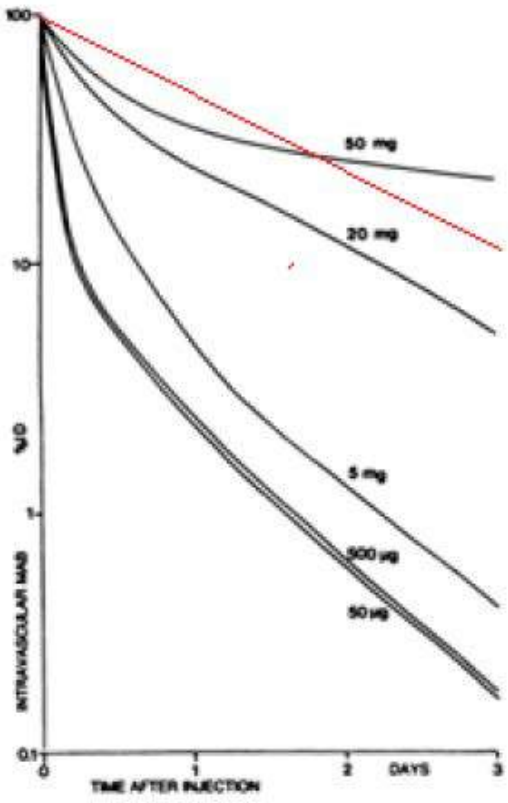


Ex. 1052, 249 (Fig. 1). The figure above shows "[t]ypical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues." *Id.*

We do not find that the expected profile for receptor-mediated drug disposition, as shown in Levy, supports the reasonableness of Dr. Jusko's pharmacokinetic analysis for trastuzumab. Levy does not describe the kinetics of antibodies at all, but instead only identifies certain small molecules that might exhibit this "hypothetical behavior." Ex. 2084, 22:10–16, 59:8–16. Specifically, with reference to Figure 1 shown above, Levy notes that "the effect on pharmacokinetics can be quite striking in that the plasma concentration profile exhibits a terminal decay phase with a very long half-life ($t_{1/2}$), as is the case for certain angiotensin-converting enzyme (ACE) and aldose reductase inhibitors." Ex. 1052, 248. In criticizing Dr. Grass's reliance on the indisulam data discussed above, Dr. Jusko notes that skilled artisans would not "rely[] on pharmacokinetic behavior of ***small molecules***, which was known to be fundamentally different to that of antibodies." Ex. 1057 ¶ 5; *see also id.* ¶ 20 n.1 (noting "in addition to the

[differences in] molecular weight, the different mechanisms of disposition of small molecules and antibodies impacts their pharmacokinetic profiles"). Accordingly, we are not persuaded by Dr. Jusko's inconsistent opinion relying upon Levy's teachings with respect to target-mediated disposition of small molecules. Ex. 1057 ¶ 15. Moreover, even with respect to the ACE inhibitors discussed therein, Levy does not make any definitive conclusions as to their pharmacokinetic behavior, noting instead that "[m]ore definitive information can be obtained only in animal studies that permit opening of the 'black box' to explore what goes on in individual tissues." Ex. 1052, 248–49.

Petitioners also point to the following graph from Koizumi, *et al.*, *Multicompartmental Analysis of the Kinetics of Radioiodinated Monoclonal Antibody in Patients with Cancer*, 27(8) J. NUCLEAR MED. 1243–54 (1986) (Ex. 1054) ("Koizumi"):



Reply, 22; Ex. 1054, 1252 (Fig. 8) (annotation in red added by Petitioners). The annotated figure above shows "[m]odel simulated curves" for intravascular monoclonal antibodies (MAb) reflecting the "effect of different amount of injected MAb on blood clearance." *Id.* According to Petitioners, "for a given antibody dose (here 50mg), a linear model (shown in red) would underestimate the actual serum concentration (shown in black) soon after dosing." Reply 21.

We do not find that Koizumi supports the reasonableness of Dr. Jusko's application of a linear model. Indeed, Petitioners' own annotation in the figure above shows that a linear model could overestimate actual serum concentrations for certain doses (e.g., 20 mg) or at certain times after injection (e.g., less than 2 days). For tri-weekly trastuzumab administration, it was unknown whether the actual serum concentration would fall above or

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 68. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 64.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. We have not relied upon Exhibits 1043–1048, 1050, and 1055 in rendering this decision. We have not given any weight to this evidence to support Petitioners' obviousness arguments because they have publication dates after August 27, 1999, and thus do not qualify as prior art to the '379 patent. *See* Paper 64, 7–10 (explaining why post-priority date references relied upon by Petitioners are irrelevant to obviousness determination in this proceeding). Furthermore, Exhibit 1055 has not been cited or relied upon by Petitioners in their Reply, and we decline to incorporate by reference the opinion in Dr. Jusko's reply declaration concerning that exhibit. *See* 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Accordingly, we dismiss as moot Patent Owner's motion to strike this evidence.

We have taken into consideration Exhibits 1052 and 1054 in our analysis, as discussed above. We determine that these exhibits and Petitioners' arguments in relation to these exhibits are proper reply evidence as they seek to respond to Patent Owner's arguments concerning the reasonableness of Dr. Jusko's pharmacokinetic analysis. Specifically, in relying upon Exhibits 1052 and 1054, and the portions of Dr. Jusko's reply declaration citing those exhibits, Petitioners seek to respond to Patent Owner's criticism that Dr. Jusko's assumptions would have overestimated

serum concentration for dose-dependent drugs such as trastuzumab. With such evidence, Petitioners seek to further support, not modify, their basis for reasonable expectation of success set forth in the Petition. We do not find that Petitioners have presented an "entirely new rationale" worthy of being excluded in their Reply. *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, *6 (Fed. Cir. Aug. 27, 2018). Although we find the new exhibits unpersuasive, that does not render them improper reply evidence. We, therefore, deny Patent Owner's motion to strike this evidence.

IV. CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioners have shown that a skilled artisan would have been motivated to extend the dosing frequency of trastuzumab from weekly to tri-weekly, Petitioners have not met their burden to show a reasonable expectation of success with respect to such a dosing regimen. As a result, Petitioners have not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent would have been obvious over the combination of the Herceptin Label, Baselga '96, Pegram '98, and the knowledge of the skilled artisan.

V. ORDER

Accordingly, it is:

ORDERED that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent have not been shown to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

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

IPR2017-00805
Patent 7,371,379 B2

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EXHIBIT 11

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Paper No. 69
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01140
Patent 7,371,379 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Granting Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")), requesting an *inter partes* review of claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of U.S. Patent No. 7,371,379 B2 (Ex. 1001, "the '379 patent"). We instituted trial to review patentability of the challenged claims.[1] Paper 31 ("Dec.").

Genentech, Inc. ("Patent Owner") filed a Response to the Petition (Paper 27, "PO Resp."), and Petitioner filed a Reply (Paper 40). The parties also briefed whether certain exhibits should be excluded from the record. Papers 52, 54, 56, 57, 59, 61. In addition, the parties briefed whether certain evidence and argument presented by Petitioner exceeded the proper scope of the Reply. Papers 53, 58, 62. Furthermore, Patent Owner filed a motion for observation on the cross-examination of Petitioner's declarant (Paper 55), and Petitioner filed an opposition thereto (Paper 60).

An oral hearing for this proceeding was held on May 8, 2018. *See* Paper 66.

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent are unpatentable.

[1] We inadvertently omitted claims 13–15 in the original Decision to Institute dated October 4, 2017. On January 25, 2018, we reissued the Decision to correct that mistake.

Related Proceedings

The '379 patent is also the subject of IPR2017-00805. Concurrently with this Decision, we issue a final written decision in that case.

We also issue, concurrently with this Decision, final written decisions in IPR2017-00804 and IPR2017-01139 to address the patentability of certain claims of U.S. Patent No. 6,627,196, a patent in the same family of the '379 patent at issue here.

The '379 Patent

The '379 patent claims priority to a provisional application filed August 27, 1999. Ex. 1001, (60).

The '379 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:15–16. According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:44–49. Before the '379 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers. *Id.* at 3:59–65. The recommended initial "loading dose" for Herceptin® was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:66–4:3.

The invention described in the '379 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:26–31. According to the '379 patent, "the method of treatment involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:51–55. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:66–5:2. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 µg/ml and does not fall below 0.01 µg/ml during treatment." *Id.* at 5:4–9.

The '379 patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:9–12. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:31–34. Additionally, it states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and subsequent doses are separated from each other by at least about two weeks, and optionally at least about three weeks. *Id.* at 6:23–34.

The '379 patent describes embodiments in which the initial dose of anti-ErbB2 is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 µg/ml during the treatment period. *Id.* at 5:19–43, 45:19–45. The treatment regimen according to the invention may further comprise administration of a chemotherapeutic agent, such as a taxoid, along with the anti-ErbB2 antibody. *Id.* at 6:6–10, 7:26–32, 46:28–58.

Of particular relevance, the '379 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:60–48:32. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [µ]g/ml, in the range (10–20 [µ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 47:1–5. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '379 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:28–31.

Illustrative Claims

Among the challenged claims, claims 1 and 30 are independent, and are reproduced below:

> 1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

> administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
>
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and
>
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.
>
> 30. A method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses of the antibody, wherein the subsequent doses are separated from each other in time by at least about two weeks, and further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Reviewed Ground of Unpatentability

We instituted *inter partes* review to determine whether the challenged claims would have been obvious over the combination of Slamon,[2] Watanabe,[3] Baselga,[4] and Pegram.[5]

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[2] D. Slamon et al., *Addition of Herceptin(™) (Humanized Anti-HER2 Antibody) to First Line Chemotherapy for HER2 Overexpressing Metastatic Breast Cancer (HER2 +/MBC) Markedly Increases Anticancer Activity: A Randomized Multinational Controlled Phase III Trial*, 17 J. CLIN. ONCOL. 98a, Abstract *377 (1998) (Ex. 1005).

[3] T. Watanabe et al., *Pharmacokinetically Guided Dose Escalation Study of Anti-HER2 Monoclonal Antibody in Patients with HER2/NEU-Overexpressing Metastatic Breast Cancer*, 17 JOURNAL OF CLINICAL ONCOLOGY 182a, Abstract *702 (1998) (Ex. 1006).

[4] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1007).

[5] Pegram, et al., *Phase II Study of Receptor-Enhanced Chemosensitivity*

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Mark J. Ratain (Exs. 1003, 1123), and Patent Owner relies on the Declarations of Dr. George M. Grass and Dr. Karen A. Gelmon (Exs. 2027, 2028).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Decision to Institute, we stated that we see no need to expressly construe any claim terms. Dec. 6–7 (citing *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating claim terms need only be construed to the extent necessary to resolve the controversy)). During trial, the parties do not argue otherwise, and we see no reason to change our

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Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment, 16 J. CLIN. ONCOL. 2659–71 (1998) (Ex. 1009).

position. Thus, on this record and for purposes of this Decision, we do not expressly construe any claim terms.

Prior Art Disclosures

Slamon

Slamon summarizes the results of a Phase III clinical trial in which patients received Herceptin (H) along with chemotherapy (CRx). Ex. 1005, 5. The chemotherapy (doxorubicin-cyclophosphamide or paclitaxel) was administered once every three weeks. *Id.* The Herceptin was administered intravenously at a 4 mg/kg loading dose, followed by 2 mg/kg weekly doses. *Id.* Slamon indicates that "[a]t a median follow-up of 10.5 months, investigator assessments of time to disease progression (TTP) and response rates (RR) show a significant augmentation of CRx effect by H, without increase in overall severe adverse events (AE)." *Id.* As such, Slamon concludes that the data from the clinical trial "indicate that addition of Herceptin to CRx markedly increases clinical benefit, as assessed by RR and TTP." *Id.*

Watanabe

Watanabe summarizes a phase I dose escalation study of an anti-HER2 monoclonal antibody (MAb 4D5 (MKC-454)) in patients with chemotherapy-resistant metastatic breast cancer. Ex. 1006, 5. In the study, the first dose of antibody was followed in 3 weeks by 9 weekly doses. *Id.* Doses of 1, 2, 4, and 8 mg/kg were administered as 90-minute intravenous infusions. *Id.* Watanabe provides data regarding patients receiving the different dosages of anti-HER2:

MKC454 dose	# of Pts	trough level (μg/ml)	toxicity		tumor response
			grade 2	grade 3≤	
1 mg/kg	6	9		1 fever, 1 n/v	
2 mg/kg	3	19	1 fever, 1 pain		1 MR
4 mg/kg	3	102	1 fever		1 PR
8 mg/kg	6	248		1 pain	1 MR, 2 PR

Id. The chart above reports the trough level, toxicity, and tumor response. According to Watanabe, "[t]arget trough plasma concentration was achieved with 2 mg/kg weekly intravenous infusions." *Id.* Thus, Watanabe concludes that "[f]urther clinical trials examining the efficacy of MAb 4D5 (MKC-454) with 2–4 mg/kg weekly intravenous infusions is warranted." *Id.*

Baselga

Baselga reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1007, 3. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 4. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to Baselga, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at 3. Out of the 768 times rhuMAb HER2 was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 5. Baselga also teaches that "[i]n preclinical studies, both in vitro and in xenografts, rhuMAb HER2 markedly potentiated the antitumor effects of

several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 9.

Pegram

Pegram reports the results of a phase II clinical trial using a combination of rhuMAb HER2 plus cisplatin. Ex. 1009, 2. It states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 3. It also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that rhuMAb HER2 did not increase toxicity. *Id.* at 11.

Level of Ordinary Skill in the Art

According to Petitioner,

> A POSA to whom the '379 patent is directed would have had either an M.D. with subspecialty training in oncology and/or a Ph.D. with substantial experience in oncology drug development. Such an individual would also have had familiarity with the treatment of breast cancer and substantial experience in the design and/or implementation of oncology clinical trials, as well as expertise in clinical pharmacology, including pharmacokinetics.

Pet. 15 (citations omitted). "Patent Owner does not dispute the areas of substantive expertise," but adds that "[a] skilled artisan would have had access to and worked on a team with a number of other individuals involved in drug development with expertise in clinical pharmacology, including pharmacokinetics." PO Resp. 23–24 (citation omitted).

We do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision. We further note that, in this case,

the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown").

Obviousness Analysis

Petitioner contends that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram. Pet. 28–60. After reviewing the entire record, we determine that Petitioner has not established by a preponderance of the evidence that the challenged claims are unpatentable.

For claim 1, Petitioner refers to Slamon for teaching an effective treatment regimen that combined Herceptin with chemotherapy, wherein Herceptin was administered at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. Pet. 28 (citing Ex. 1005, 5). Petitioner argues that an ordinary artisan "would have been motivated to administer trastuzumab as disclosed by Slamon, but would have recognized that weekly administration would be inconvenient for patients, who otherwise would need infusions only once every three weeks."[6] *Id.* at 28–29 (citing Ex. 1003 ¶ 89; Ex. 1017, 1–4). Petitioner contends that an ordinary artisan "would have sought to reduce the frequency of trastuzumab administration to align it with the less arduous chemotherapy regimen in

[6] Even though some claims only require administering trastuzumab once every two weeks, our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

order to improve patient convenience." *Id.* at 29 (citing Ex. 1003 ¶ 90). When modifying the dosing schedule, according to Petitioner, an ordinary artisan "would have recognized the importance of maintaining dose intensity" and would have administered an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses, each administered three weeks apart. *Id.* at 29–30 (citing Ex. 1003 ¶ 91).

With regard to safety concerns, Petitioner contends that based on Watanabe's disclosure that weekly doses as high as 8 mg/kg were safe and well-tolerated, an ordinary artisan "would not have expected an increase in toxicity, or any other safety concerns, for the higher doses required by the every three week regimen." *Id.* at 31 (citing Ex. 1006, 5; Ex. 1003 ¶¶ 72, 92–93). Petitioner emphasizes that "the overall number of severe adverse events was in fact ***lower*** for the six patients treated at the 8 mg/kg dose than Watanabe disclosed for the 1 mg/kg dose." *Id.* Petitioner also cites other prior art references as teaching that trastuzumab was safe at doses as high as 8 mg/kg. *Id.* at 31 (citing Ex. 1008, 1; Ex. 1013, 4; Ex. 1014, 4; Ex. 1012, 11:54–56; Ex. 1015, 2:60–61; Ex. 1018, 48:19–52).

With regard to efficacy, Petitioner relies upon the prior art's disclosure of a target serum concentration (trough concentration) of 10 µg/ml. *Id.* at 33 (citing Ex. 1003 ¶ 96; Ex. 1006, 5; Ex. 1007, 4; Ex. 1009, 3). In determining whether the every-three-week regimen would satisfy this trough concentration, Petitioner relies upon the disclosures in Baselga and Pegram that trastuzumab has a mean half-life of at least one week. *Id.* at 34 (citing Ex. 1003 ¶ 103; Ex. 1007, 5; Ex. 1009, 8). Petitioner argues that because "Baselga further discloses that trastuzumab has dose-dependent pharmacokinetics," an ordinary artisan "would have understood

that its half-life would actually be longer at higher doses." *Id.* at 34–35 (citing Ex. 1003 ¶ 102; Ex. 1007, 3). Thus, Petitioner contends that "the serum concentration would decrease by half no more than three times" before the next 6 mg/kg maintenance dose is administered. *Id.* at 35 (citing Ex. 1003 ¶¶ 104–105). Based on an initial serum concentration of 169 µg/ml (calculated based on Pegram's disclosure), Petitioner estimates that approximately 21.1 µg/ml would remain after three weeks, which is above the 10 µg/ml trough concentration required for efficacy. *Id.* at 35–36 (citing Ex. 1003 ¶¶ 100, 104). Petitioner comes to a similar conclusion based on the pharmacokinetic data disclosed in the 1998 Herceptin label. *Id.* at 38–39.

Patent Owner counters that an ordinary artisan would not have been motivated to administer trastuzumab in accordance with the claimed regimen. PO Resp. 26–42. Patent Owner also contends that Petitioner has not established "a reasonable expectation of success that extending the trastuzumab dosing regimen to three weeks with the claimed loading and maintenance doses would be safe and effective." *Id.* at 42–58.

Motivation to Modify

Dosing Frequency

Patent Owner asserts that an ordinary artisan would not have been motivated to administer trastuzumab on the every-three-week dosing schedule. PO Resp. 26–42. We are not persuaded.

Patent Owner asserts that an ordinary artisan "would not have been motivated to extend the dosing interval for the sake of convenience." *Id.* at 26. According to Patent Owner, in August 1999, the priority date of the

'379 patent, an ordinary artisan would have been focused on improving efficacy of trastuzumab, and not convenience. *Id.* at 24, 26–28. We are not persuaded.

As a preliminary matter, we agree with Patent Owner that none of the asserted prior art references individually teaches the claimed dosing schedule explicitly. *See id.* at 17–23. Non-obviousness, however, cannot be established by attacking references individually where the patentability challenge is based upon the teachings of a combination of references. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Here, as explained below, the prior-art teachings as a whole, together with the knowledge of one of ordinary skill in the art, would have motivated an ordinary artisan to modify the dosing schedule of trastuzumab in order to improve patient convenience.

Patent Owner contends that Petitioner bases the obviousness challenge on a "generalized concern for 'convenience' untethered to the specific patient population of the claims." PO Resp. 29. According to Patent Owner, HER2-positive breast cancer is a serious, life-threatening disease, and "[p]atients thus need little additional convincing in the form of convenience to take trastuzumab." *Id.* at 36–37 (citing Ex. 2028 ¶¶ 42–47), *see also id.* (citing Ex. 2028 ¶¶ 50, 57) (arguing "compliance was not likely to be an issue for breast-cancer patients"). We are not persuaded.

First, except claims 17 and 18, the other challenged claims are not limited to breast cancer. *See* Ex. 1001, 58:56–65 (dependent claim 16 reciting the cancer is selected from at least 24 different types of cancer, including small-cell lung cancer and colorectal cancer), *see also id.* at 15:33–35 ("Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia."). Second, the record reflects

that some patients, despite having metastatic breast cancer, and even in the context of a tightly controlled clinical study, in fact missed treatment due to reasons such as "social obligations" and other "commitments." Ex. 2016, 3355. Thus, prior art suggests convenience and compliance are important, even among patients with metastatic breast cancer.

Patent Owner argues that "[n]othing in the prior art suggests that skilled artisans treating patients with HER2-positive cancer were concerned with convenience in August 1999." PO Resp. 24. But the prior art relied upon by Petitioner need not expressly articulate or suggest patient convenience as a motivation to extend the dosing interval. Indeed,

> The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. As [the Federal Circuit] explained . . . "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1361 (Fed. Cir. 2006) (internal citations omitted).

Patent Owner is correct that one of ordinary skill in the art would have considered efficacy critical in treating cancer. PO Resp. 26–27. Efficacy, however, is not the sole consideration. *See, e.g.*, Ex. 1103, 1 (stating that a new regimen for treating small-cell lung cancer was designed with the objectives to "maintain efficacy, diminish toxicity, enhance compliance, and improve chemotherapy administration convenience at an acceptable cost").

Indeed, in 1998, the FDA issued the Guidance for Industry regarding "New Cancer Treatment Uses for Marketed Drug and Biological Products." Ex. 1118. According to the guideline, "[n]ew dosing regimens (including

changes in the range of doses administered for approved indications and changes in the schedule of administration) can lead to improved effectiveness, tolerance, or convenience." *Id.* at 8.

Dr. Gelmon, an expert for Patent Owner, does not disagree. *See, e.g.*, Ex. 1104, 81:10–15 (testifying that when exploring an alternative dosing schedule, a clinician treating a cancer patient would look at efficacy, safety, and quality of life, "[a]nd one of the factors that comes in after those things is always [the] effect on the patient including convenience"). This approach had been borne out by data from clinical trials. For example, in an article Dr. Gelmon co-authored, the researchers studied bi-weekly paclitaxel as first-line treatment for metastatic breast cancer in a phase I-II trial. Ex. 1101, 1. Based on the results, they concluded that "[t]he good drug tolerance, response rates, and convenience over weekly treatment suggest this may be a worthwhile regimen." *Id.*, *see also id.* at 3 ("The tolerance is similar to the weekly schedule but bi-weekly paclitaxel may be more convenient.").

Other prior art of record confirms that convenience was a motivating factor in exploiting new dosing regimens. Often, after a drug is introduced into clinical trials, an ordinary artisan would pursue different clinical strategies "in an attempt to identify the schedule with the optimal balance between clinical activity, safety, and convenience." Ex. 1017, 2 (discussing alternative dosing schedules for an anti-cancer drug in clinical trials for colorectal cancer, including a weekly schedule and an every-three-week schedule). When developing new dosing strategies for an anti-cancer drug, an ordinary artisan would take into account biology, pharmacology, and toxicity of the drug, as well as pragmatic factors, "including the regimen's

cost, convenience, and ease of compliance. An additional pragmatic consideration is how well the schedule accommodates other drugs . . . that will be given with [the drug-at-issue]." *Id.* at 1–2.

Here, Slamon teaches the results of a combination therapy in which Herceptin "markedly increases anticancer activity" of chemotherapy in HER2 overexpressing metastatic breast cancer. Ex. 1005, 5. In that phase III clinical trial, chemotherapy was administered every three weeks, whereas Herceptin was administered weekly. *Id.* Herceptin Product Label teaches the same. Ex. 1008. In late 1998, the FDA approved Herceptin for treating patients with metastatic breast cancer whose tumors overexpress the HER2 protein. *Id.* at 1. As a first-line treatment, Herceptin is to be used in combination with paclitaxel. *Id.* Paclitaxel is administered once every three weeks, and Herceptin is administered weekly. *Id.* Citing the Declaration of Dr. Ratain, Petitioner argues that an ordinary artisan would have recognized that weekly administration of trastuzumab would be inconvenient for patients, and would have sought to reduce the frequency of trastuzumab administration to that of paclitaxel in order to improve patient convenience. Pet. 28–29 (citing Ex. 1003 ¶¶ 89, 90; Ex. 1017, 1–4).

Patent Owner contends that "Dr. Ratain did not cite any evidence to support these assertions." PO Resp. 29. That, however, is not fatal to Petitioner's position, because an obviousness analysis "not only permits, but *requires*, consideration of common knowledge and common sense." *DyStar*, 464 F.3d at 1367. Furthermore, as discussed above, Petitioners have supported Dr. Ratain's opinions with citations to the prior art. Relying on this prior art, Petitioner argues that "a once every three week regimen 'has the added advantage of greater patient convenience, as it entails less frequent

dosing than is required on a weekly schedule.'" Pet. 29 (citing Ex. 1017, 1–4). Having established that this knowledge was in the art, Dr. Ratain and Petitioner "could then properly rely . . . on a conclusion of obviousness from common knowledge and common sense of the person of ordinary skill in the art without any specific hint or suggestion in a particular reference." *DyStar*, 464 F.3d at 1368 (internal quotation marks omitted).

Patent Owner argues that at the time of the '379 patent, "treatment with weekly trastuzumab could ***improve*** patient quality of life in comparison to treatment with chemotherapy regimens alone, despite the weekly regimen." PO Resp. 27. Patent Owner misses the point. It is undisputed that weekly trastuzumab was known to be efficacious and thus, could improve quality of life for patients in comparison to chemotherapy treatment alone. The proper comparison here though, is not weekly trastuzumab versus chemotherapy regimens, but every-three-week versus weekly trastuzumab.

Patent Owner also asserts that "[s]killed artisans at the time of the invention were motivated by trastuzumab's Phase III results to explore the weekly co-administration of trastuzumab and paclitaxel—not extending trastuzumab to match paclitaxel." PO Resp. 32. Even if this were true, it would not have dissuaded an ordinary artisan from pursuing a regimen to administer trastuzumab every three weeks. That is because, in an obviousness analysis, "the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination," not whether the prior art suggests the combination as the most desirable combination available. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (quotation marks and alteration omitted).

Moreover, the only paclitaxel dosing regimen approved by the FDA for treating breast cancer was, and still is, one administered every three weeks. Ex. 1117, 6. Even in the references Patent Owner points to, the ordinary artisan recognized that paclitaxel is effective on either an every-three-week or weekly schedule. Ex. 2036, 385. In addition, "a dose of 175 mg/m^2 by 3-h infusion every three weeks appears to be very reasonable in the treatment of advanced breast cancer. In combination therapy, this dose is often easily combined with other agents, producing manageable toxicity and not usually requiring hematopoietic growth factor support." *Id.* In the challenged '379 patent, paclitaxel is indeed combined with another agent, trastuzumab. Thus, even if an ordinary artisan had tried, or would have preferred, to decrease the dosing interval of paclitaxel to weekly to match that of trastuzumab, we are persuaded that the artisan would also have been motivated to extend the dosing interval of trastuzumab to every three weeks to match that of paclitaxel.

Dosage Amount

Each of claims 1–3, 5, 7, 9–11, and 13–28 requires, either explicitly or through dependency, "an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody," and "a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose." Ex. 1001, 56:63–67. In addition, each of claims 33 and 38 requires at least two or more subsequent doses that "are each from about 4 mg/kg to about 12 mg/kg," and each of claims 34 and 39 requires at least two or more subsequent doses that "are each from about 6 mg/kg to about 12 mg/kg." Patent Owner argues the prior art does not suggest the claimed loading and

maintenance doses. PO Resp. 37–42. After reviewing the entire record, we agree that Petitioner has not met its burden in this regard.

As an initial matter, we are not persuaded by Patent Owner's contention that "the prior art's statements that weekly dosing of trastuzumab was 'optimal' (Ex. 1007 at 4) and 'warranted' (Ex. 1006 at 5) would have pointed a skilled artisan away from three-week dosing." PO Resp. 37. Prior art may not teach away even if a particular solution is not the preferred solution or is inferior to another solution. *In re Fulton*, 391 F.3d at 1200. Instead, a reference teaches away if it criticizes, discredits, or otherwise discourages the solution claimed. *Id.* at 1201.

Here, Dr. Gelmon, an expert for Patent Owner, testified that even after a drug is approved, an ordinary artisan would keep on optimizing the dosing regimen by "changing schedule or changing dosing." Ex. 1104, 64:16–65:4. As explained above, an ordinary artisan would have been motivated to modify the dosing frequency in order to improve patient convenience. And an ordinary artisan would have adjusted the dosage amount accordingly. Thus, just because Watanabe and Baselga described the dosage amount of trastuzumab for a **weekly** dosing regimen as "optimal" or "warranted" would not have dissuaded an ordinary artisan from adjusting the dosage amount for an every-three-week dosing regimen.

We, however, find Petitioner has not met its burden in addressing the motivation for an ordinary artisan to modify the loading and the maintenance dosage as the challenged claims require. Petitioner asserts that "[w]hen modifying the dosing schedule, a POSA would have recognized the

importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 29 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). According to Petitioner,

> As shown in the table below, when accounting for dose intensity, Slamon's trastuzumab regimen calls for administration of a total of 8 mg/kg over the first three week period, followed by 6 mg/kg every three weeks thereafter:

week	1	2	3	4	5	6	7	8	9	10	11	12
weekly dose (mg/kg)	4	2	2	2	2	2	2	2	2	2	2	2
q 3 week dose (mg/kg)	8			6			6			6		

Id. at 29–30 (citing Ex. 1005, 5; Ex. 1003 ¶ 91).

Patent Owner argues that this approach is flawed because "Petitioner has failed to articulate ***why*** a skilled artisan would apply a chemotherapy dosing strategy to trastuzumab, a targeted antibody treatment." PO Resp. 40 (citing Ex. 2028 ¶ 58). We find Patent Owner's argument persuasive.

When resorting to the principle of "dose intensity," Petitioner and Dr. Ratain initially relied on Exhibits 1024 and 1029. Pet. 29 (citing Exs. 1024, 1029); Ex. 1003 ¶ 91 (citing Ex. 1024, 1; Ex. 1029, 9–10). Both of those two references, however, describe the dosing of doxorubicin, a chemotherapy agent. *See* Exs. 1024, 1029. In response to Patent Owner's challenge that dose intensity is a chemotherapy dosing strategy, Petitioner contends that "POSAs understood that the concept of dose intensity was applicable to a variety of oncology drugs, including targeted antibodies." Reply 15–16 (citing Ex. 1123 ¶ 36; Exs. 1111, 1121, 1126); Ex. 1123 ¶ 36 (citing Exs. 1111, 1121, 1124, 1125, 1126, 1130).

Among the references submitted with the Reply to support the applicability of the concept of dose intensity in this case, only Cheson[7] is directed to an antibody. Cheson teaches Mabthera, an anti-CD20 antibody, "demonstrated activity in intermediate-grade NHL, mantle cell lymphoma, lymphoplasmacytic NHL, and post-transplant lymphoproliferative disorder." Ex. 1126, 4. According to Cheson, "[l]ower response rates in small lymphocytic NHL and CLL, reflecting the low density of CD20 on the malignant cells, may be overcome by **increasing the dose intensity** of Mabthera." *Id.* (emphasis added). Read in this context, the phrase "dose intensity," as used in Cheson, appears to refer to the amount of a single dose, rather than "the amount of drug administered **over a period of time**," as that phrase defined by Petitioner. *See* Pet. 29 (emphasis added). Thus, we agree with Patent Owner that Petitioner has not "cite[d] any evidence that skilled artisans would have applied the concept of 'dose intensity' to antibody treatment." *See* PO Resp. 40.

Petitioner contends that "[t]here was nothing in the prior art about trastuzumab that would have dissuaded a POSA from using the approach of keeping the same dosage amount over time," and "Patent Owner has failed to identify any alternative approach to dose selection that would have been appropriate." Reply 16–17. But it is not Patent Owner's burden to identify an "alternative approach." Rather, Petitioner must prove unpatentability by a preponderance of the evidence (*see* 35 U.S.C. § 316(e); 37 C.F.R.

[7] B. Cheson, *Future Perspective: Mabthera® in the Next Millennium*, Abstracts of Satellite Symposia, Mabthera Future Applications In CD20+ Malignancies (June 1, 1999) (Ex. 1126).

§ 42.1(d)), and that burden never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Patent Owner asserts that because the goal of antibody dosing is different from that of chemotherapy dosing, an approach that would be desired for chemotherapy may not be necessarily a desired one when administering an antibody. PO Resp. 5–7, 40–41; *see also* Ex. 2028 ¶ 58 ("In 1999, oncologists did not know enough about trastuzumab's mechanism of action to feel comfortable automatically applying principles from chemotherapy dosing to trastuzumab dosing.").

According to Patent Owner, at the time of the '379 patent invention, "the goal of most chemotherapy dosing was to kill the greatest number of tumor cells without causing life-threatening toxicity." *Id.* at 5 (citing Ex. 2028 ¶¶ 30–31). This was achieved, Patent Owner continues, by administering "the highest tolerable dose (typically resulting in a high peak concentration) followed by sufficient time for recovery (and very low troughs)." *Id.* at 41 (citing Ex. 2028 ¶ 31). Dr. Ratain does not appear to disagree. Ex. 2026, 54:12–59:6.

In contrast, Patent Owner argues, "at the time of the invention, skilled artisans believed that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval." *Id.* at 41 (citing Ex. 2028 ¶ 36); *see also* Ex. 2027 ¶¶ 45–47 (Dr. Grass testifying that an ordinary artisan would "want to ensure that any alternative dosing regimen maintained therapeutic trough concentrations throughout the course of treatment"). The prior art confirms this. *See, e.g.*, Ex. 1006, 5 (setting 10 μg/ml as the target trough plasma concentration); Ex. 1007, 4 ("The

pharmacokinetic goal was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth in the preclinical model.").

As Petitioner's expert, Dr. Ratain, explains, for a drug at a given total cumulative dose, "as the intervals between doses increase, the fluctuation increases, with higher peaks and lower trough concentrations." Ex. 1003 ¶ 57. In view of the prior-art teaching that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval, this testimony by Dr. Ratain casts doubt as to whether an ordinary artisan would have applied the concept of dose intensity to an antibody treatment, such as trastuzumab.

Further compounding the complexity of the issue is the presence of shed antigen. At the relevant time, it was known that

> Detectable concentrations of the circulating extracellular domain ["ECD"] of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Ex. 1008, 1. *See also* Ex. 1009, 8 ("[P]atients with any measurable shed HER2/*neu* ECD serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations . . . across all time points.").

Accordingly, considering (1) the lack of sufficient evidence from Petitioner to show that an ordinary artisan would have applied the concept of dose intensity to an antibody treatment; (2) the presence of shed antigen, which shows an inverse relationship to serum trough concentration; (3) the

acknowledgment by Dr. Ratain that "there were not enough publications about trastuzumab . . . for those [dose-intensity] analyses to be presented" (Ex. 2026, 64:8–10); and (4) the testimony of Dr. Ratain that "the rationale that would lead [an ordinary artisan] to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks" (*id.* at 59:13–18), we conclude that Petitioner has not met its burden to demonstrate that an ordinary artisan would have had a reason to modify the loading and maintenance doses as claimed.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–28, 33, 34, 38, and 39 of the '379 patent are unpatentable. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Reasonable Expectation of Success

Claims 30, 31, 35, 36, and 40 do not recite either the first or any subsequent dosage amount of trastuzumab. In addition, claims 32 and 37 require at least two or more subsequent doses "are each from about 2 mg/kg to about 16 mg/kg." As explained above, we find an ordinary artisan would have been motivated to modify the dosing frequency of trastuzumab as claimed. In addition, both Slamon and Herceptin Product Label teach the loading dose of 4 mg/kg and the maintenance doses of 2 mg/kg. Ex. 1005, 5; Ex. 1008, 2. Even so, we find Petitioner has not established by a preponderance of the evidence that claims 30–32, 35–37, and 40 of the '379 patent are unpatentable. This is because Petitioner's analysis of these claims hinges on the same argument of 8 mg/kg loading dose and 6 mg/kg

maintenance doses Petitioner asserts in the other claims. For example, the substantive analysis of claim 30, in its entirety, appears in a single paragraph:

> As discussed above with respect to claim 1, it would have been obvious to administer trastuzumab on an every-three-week regimen as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses. *See also* Ex. 1003 at ¶¶ 89–112. This regimen would have satisfied each and every element of claim 30 of the '379 patent, and therefore claim 30 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶¶ 89–112, 115–118.

Pet. 45.

For claim 1, Petitioner analyzes the reasonable expectation of success with respect to efficacy based on an 8 mg/kg loading dose and 6 mg/kg maintenance doses. Pet. 33–39, 43–44. Because Petitioner has not met its burden to show that an ordinary artisan would have been motivated to modify the dosage amount in the first instance, its reasonable-expectation-of-success arguments, premised upon efficacy associated with administering those modified dosage amounts over the every-three-week dosing frequency, also fail.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 30–32, 35–37, and 40 of the '379 patent are unpatentable.

Motions to Exclude

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2004, 2039, 2041, 2061, 2062, and 2067. Paper 52. Patent Owner does not oppose. Paper 56.

Petitioner's Motion to Exclude is granted.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1100, 1102, 1105, 1107, 1111, 1121, 1124, 1125, 1126, 1128, and 1130, as well as paragraphs 22, 29, 35–37, 44, 53–58, and 60–73 of Exhibit 1123, i.e., the Reply Declaration of Dr. Ratain. Paper 54. Patent Owner filed an Identification of Improper New Reply Materials, challenging the same exhibits. Paper 53.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[8] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. Patent Owner argues that in paragraphs 35–37 of Ratain Reply Declaration (Ex. 1123), Dr. Ratain relies on Exhibits 1111, 1121, 1124, 1125, 1126, and 1130, and introduces new arguments related to the alleged use of the concept of dose intensity in the development of new dosing regimens. Paper 54, 1, 8–11. According to Patent Owner, these six new

[8] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

exhibits, as well as paragraphs 35–37 of Exhibit 1123 "should be excluded as improper reply evidence used to fill a gap in Petitioner's *prima facie* case." *Id.* at 1. We disagree.

"Evidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1078 (Fed. Cir. 2015). Such is the case here.

In the Petition, citing the Declaration of Dr. Ratain, Petitioner argues that "[w]hen modifying the dosing schedule, a POSA would have recognized the importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 29 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). In its Response, citing the Declaration of Dr. Gelmon, Patent Owner counters that an ordinary artisan would not have relied on the concept of dose intensity because it is a chemotherapy concept, whereas trastuzumab, an antibody, works differently from a chemotherapy agent. PO Resp. 40–41 (citing Ex. 2028 ¶¶ 31, 36, 58).

In his Reply Declaration, Dr. Ratain relies on the challenged exhibits to support his opinion that the concept of dose intensity "is applicable to other therapeutic areas and contexts," including antibodies. Ex. 1123 ¶¶ 35–37 (citing Ex. 1111, 1121, 1124, 1125, 1126, 1130). Thus, paragraphs 35–37 in the Ratain Reply Declaration, as well as the exhibits relied on therein, respond directly to Patent Owner's criticism of the dose-intensity principle. With such evidence, Petitioner intends to confirm, not to modify, its prima facie case. Although we find the new exhibits unpersuasive, that

does not render them improper reply evidence. We, therefore, deny Patent Owner's Motion to Exclude regarding paragraphs 35–37 of Exhibit 1123, and Exhibits 1111, 1121, 1124, 1125, 1126, and 1130.

Patent Owner also seeks to exclude Exhibits 1100, 1102, 1105, 1107, and 1128, as well as paragraphs 22, 29, 44, 53–58, and 60–73 of Ratain Reply Declaration (Ex. 1123). Paper 53, 1–2, 5–8, 11–14. We do not rely on any of these exhibits in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude as moot.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioner has shown that an ordinary artisan would have modified the dosing frequency of trastuzumab from weekly to every-three-week, Petitioner has not met its burden to show that an ordinary artisan would have modified the dosage amounts as proposed. In addition, Petitioner has not met its burden to show a reasonable expectation of success because those arguments are solely based on its proposed loading and maintenance dosage amounts. As a result, Petitioner has not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram.

ORDER

Accordingly, it is

ORDERED that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent have not been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is granted;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

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

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EXHIBIT 12

(Redacted in Full)

EXHIBIT 13

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EXHIBIT 14

SMITH KATZENSTEIN JENKINS LLP

July 19, 2019

BY E-FILE AND HAND DELIVERY
The Honorable Colm F. Connolly
United States District Court of Delaware
844 North King Street
Wilmington, DE 19801

Re: *Genentech, Inc. v. Amgen Inc.*, C.A. No.: 18-924-CFC

Dear Judge Connolly,

Amgen is reviewing Genentech's filings this morning and intends to respond by Monday, July 23.

Amgen respectfully requests the opportunity to respond to the latest pleading in Genentech's recent flurry of alleged "emergency" filings, which resulted from Genentech's election to delay seeking injunctive relief as set forth more fully in Amgen's Combined Opposition to Genentech's Emergency Motion for a Temporary Restraining Order and Preliminary Injunction, D.I. 285, at 8-10.

Respectfully,

/s/ Neal C. Belgam

Neal C. Belgam (#2721)

cc: All Counsel of Record

EXHIBIT 15

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, *Plaintiffs*, v. AMGEN INC., *Defendant*.	Civ. No. 18-924-CFC

ORDER

IT IS HEREBY ORDERED, for the reasons stated in the accompanying Memorandum, that:

1. Genentech's motion for a temporary restraining order (D.I. 273) is DENIED;

2. Genentech's motion for a preliminary injunction (D.I. 274) is DENIED; and

3. The standstill order given during the July 10, 2019 teleconference is lifted.

Dated: July 18, 2019

UNITED STATES DISTRICT JUDGE

EXHIBIT 16

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, Plaintiffs, v. AMGEN, INC., Defendant.	C.A. No. 1:18-cv-00924-CFC

GENENTECH'S NOTICE OF APPEAL TO THE FEDERAL CIRCUIT

NOTICE IS HEREBY GIVEN that Plaintiff Genentech, Inc. in the above-named case hereby appeals to the United States Court of Appeals for the Federal Circuit from the Order entered in this action on July 18, 2019 (D.I. 300), insofar as such order denied Genentech's motion for a preliminary injunction.

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Dated: July 19, 2019

Respectfully Submitted,

/s/ Daniel M. Silver

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EXHIBIT 17

(Redacted in Full)

EXHIBIT 18

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EXHIBIT 19

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EXHIBIT 20

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EXHIBIT 21

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EXHIBIT 24

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EXHIBIT 25

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil No. 1:15-cv-839-RGA REDACTED PUBLIC VERSION

AMGEN'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR A PRELIMINARY INJUNCTION

Hospira may argue that it can disregard the notice requirement because the patents-in-suit (U.S. Patent Nos. 5,756,349 and 5,856,298) have expired. But that argument disregards a central purpose of paragraph (8)(A): to allow Amgen "time to make a decision about seeking relief based on *yet-to-be litigated* patents." *Apotex*, 827 F.3d at 1062 (emphasis added). By refusing to provide the manufacturing information required under § 262(*l*)(2)(A), and again refusing Amgen discovery of its manufacturing information in this case, Hospira has successfully limited Amgen's ability to detect process-patent infringement. Amgen continues to seek this information from Hospira, and the Federal Circuit will soon rule on whether Amgen can obtain this information in discovery in the present lawsuit, or otherwise assert its cell-culture patents without such information. If Hospira unlawfully launches its product without having provided to Amgen the manufacturing information required by the BPCIA, Amgen will be irreparably harmed by losing the statutory right to assess and enforce its patents for injunctive relief prior to commercial entry. "[T]he essence of a patent grant is the right to exclude others from profiting by the patented invention." *Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176, 215 (1980) (citing multiple Supreme Court cases).

3. Hospira's premature launch will cause Amgen to suffer irreparable harm in the ESA market

Amgen markets two erythropoiesis-stimulating agents ("ESAs"): EPOGEN® and ARANESP®. ESAs are used primarily to treat patients suffering from anemia in connection with chronic kidney disease (including patients on dialysis) or chemotherapy. (Billen Decl. ¶ 5; Gaier Decl. ¶¶ 20-23.) [redacted]

[redacted] Amgen also licenses a third ESA, PROCRIT®, which Johnson & Johnson ("J&J") markets to oncology clinics and other market segments other than dialysis clinics. (Billen Decl. ¶ 6; Gaier Decl. ¶ 21.) PROCRIT® contains the same active ingredient (epoetin alfa) as EPOGEN®, which Amgen manufactures for J&J, and for which Amgen receives royalties from J&J. (Billen Decl. ¶¶ 6, 21.)

Hospira's biosimilar epoetin product will compete with EPOGEN®, ARANESP®, and PROCRIT®, the three ESAs that Amgen either markets or licenses. (Billen Decl. ¶ 11; Gaier Decl. ¶ 39.) The irreparable harm that Amgen will face if Hospira prematurely launches its epoetin biosimilar product are described below and more fully detailed in the accompanying expert declaration of Eric Gaier, Ph.D.

a. Hospira's premature launch would cause Amgen to suffer irreparable price erosion

[redacted] Courts have repeatedly held that the steep loss of market share and revenue, as well as lasting price erosion, caused by the introduction of a generic drug constitute irreparable harm justifying the entry of injunctive relief. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (upholding finding of irreparable harm supporting preliminary injunction, in the form of "irreversible price erosion" due to competitor's marketing of a lower-priced generic version of patentee's drug); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm).

Medicare pays for most dialysis treatments in the United States, regardless of the age of the patient. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.) Medicare reimburses health-care providers for

dialysis services on a "capitated" or bundled basis. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.) This means that Medicare pays a single fee for each dialysis treatment, which must cover the cost of any ESA administered to patients. For this reason, healthcare providers administering ESAs in the dialysis setting have an incentive to move to lower-priced ESAs, which will enable Hospira to gain market share by aggressively pricing its epoetin product, resulting in price erosion. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.)

[redacted]

If Hospira chooses to compete with Amgen in the oncology segment, Hospira will likely offer customers discounts or rebates, which will irreparably harm Amgen. Medicare (and most private payors) reimburse doctors for oncology medication at Average Selling Price ("ASP") plus 6%. (Billen Decl. ¶ 24; Gaier Decl. ¶¶ 45-46.) The higher the ASP, the higher the physicians' profit margin. However, Hospira's newly introduced medications won't have an ASP for 6 to 9 months after launch, so Medicare will use the Wholesale Acquisition Cost, or "WAC" price, to set reimbursement in the interim. (Billen Decl. ¶ 24; Gaier Decl. ¶ 34.) If Hospira's WAC price for its newly-introduced product is greater that the ASP price of the incumbent product, Medicare reimbursement payments will be higher for the newly-introduced product. Thus, the government pays a higher price to reimburse physicians, physicians realize a higher profit margin on Hospira's reimbursements, and Amgen will be forced to lower its price to

compete. (Billen Decl. ¶ 24; Gaier Decl. ¶¶ 34-35, 45-46.)

[redacted] The law recognizes price erosion as irreparable harm due to its "irreversible effects." *Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 342-43 (S.D.N.Y. 2006), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006).

b. Hospira's premature launch would cause Amgen to suffer irreparable damage to consumer relationships and goodwill

Hospira's premature entry into the market may irreparably damage Amgen's relationship with its customers and goodwill. (Gaier Decl. ¶¶ 52-54.) If Hospira launches its biosimilar epoetin product and the Court later enjoins it based on Amgen's patent rights, Amgen's enforcing of its patent rights will be portrayed as taking a medicine off the market. If Amgen tries to raise its prices to their level before Hospira's wrongful entry, Amgen's goodwill in the market will be further harmed, particularly where reimbursement rules would likely provide doctors less than full reimbursement for the new cost after the price has been restored. In the context of patent litigation, "[t]here is no effective way to measure the loss of sales or potential growth—to ascertain the people who do not knock on the door or to identify the specific persons who do not reorder because of the existence of the infringer." *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). Here too, there is no effective way to quantify the effect of Hospira's entry into the market on Amgen's reputation.

biosimilar product that will directly compete with Amgen's EPOGEN® product, but Amgen will be denied the time and information to evaluate and secure, if appropriate, the exclusionary right that a patent uniquely grants to the inventor. The balance of the equities favor Amgen.

D. The public interest favors the entry of an injunction

There is an overriding public interest in prohibiting Hospira from disregarding the notice period in a statute enacted to encourage a predictable set of timelines to govern commercial behavior. When Congress enacted the BPCIA, it sought to strike a balance between the public interest in lower-priced biologics and the public interest in incentives for innovation. Pub. L. No. 111-148, 124 Stat. 119, 804, § 7001(b). Congress created an abbreviated FDA approval pathway for "biosimilars," effectively reducing the time and cost of bringing a competing biological product to market by allowing the applicant to rely on the clinical data and license of the innovator. Coincident with FDA review and licensure of a biosimilar product, Congress also created in the BPCIA a process for the orderly identification and enforcement of the innovator's patent rights *before* commercial marketing of the newly licensed product begins, thereby maintaining the value of patents and the incentives they provide. The public interest is best served by requiring Hospira to following the law, honoring the balance struck by Congress.

There is a strong public interest in encouraging investment in the research and development to create novel biological therapeutics that treat human disease. The fact that a copyist may sell at a lower price does not override this important public interest. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383-84 (Fed. Cir. 2006). Patents have long been recognized by the courts as an incentive to encourage just such investment: "by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research and development." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1363 (Fed. Cir. 2008) (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1974)).

EXHIBIT 26

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 16-853 (MSG)
	)	CONSOLIDATED
AMNEAL PHARMACEUTICALS LLC, et al.,	)	REDACTED - PUBLIC VERSION
	)	
Defendants.	)	

AMGEN'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR AN EMERGENCY INJUNCTION PENDING APPEAL

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Originally Filed: March 19, 2019
Redacted Version Filed: March 26, 2019

In short, there is a likelihood that the Federal Circuit will hold on *de novo* review that this Court's approach to prosecution history estoppel was contrary to settled precedent and undermines the familiar maxim that "all aspects of the prosecution must be viewed as they would be viewed by persons of skill in the field of the invention." *Hebert*, 99 F.3d at 1118.

II. Amgen Will Suffer Irreparable Harm.

It is well-known that generic entry[3] can lead to irreparable injuries like price erosion, loss of goodwill, reputational harm, and loss of business opportunities. *See, e.g.*, *Celsis*, 664 F.3d at 930. All of that is bound to happen here, as demonstrated through the attached declarations of Dr. Jerry A. Hausman and Christos Georghiou, as well as case law regarding these issues. While Piramal would be liable for damages in the event of reversal on appeal, such money damages cannot fully compensate Amgen for the well-recognized irreparable harms it will face.

A. Absent An Injunction, Generic Entry Will Destroy The SENSIPAR® Market.

"Where two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions." *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013). That is particularly true when a patent holder has been "unwilling[] to license," which also "favor[s] finding irreparable injury." *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed. Cir. 2012). The loss of market share and preferred status for a patented pharmaceutical product are both accepted forms of irreparable harm. *See, e.g.*, *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368

[3] Defendants Watson Laboratories, Inc. and Actavis Pharma, Inc. (collectively, "Watson") undertook a brief at-risk launch of its generic product in late December 2018. However, as explained in a joint motion to the Court (D.I. 412), on January 2, 2019, Amgen and Watson executed a Litigation Settlement Agreement ("the Agreement") fully resolving their respective infringement claims and invalidity counterclaims as to the '405 patent and promptly addressing Watson's launch before it caused market erosion or any other irreparable injuries to Amgen that would have occurred absent such an agreement.

(Fed. Cir. 2001); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006); *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008).

Piramal's launch will cause Amgen to incur each of these harms. Piramal will have every incentive to sell a flood of products into the distribution channels. Hausman, ¶¶ 27-28; Georghiou, ¶¶ 9-11, 25. The impact to Amgen is likely to be immediate. Typically, entry of a generic product results in immediate loss of 40% of a brand's market share, with additional losses of more than 90% over the long run. Hausman, ¶¶ 14-16. Amgen can expect a loss of up to 70% market share in the first month, and up to a 95% loss of market share within the first six months. Hausman, ¶ 22; Georghiou, ¶¶ 14, 26.

These losses are also likely to persist, because market changes to insurance coverage, reimbursement, and formulary status, as well as price erosion, are deeply engrained and almost impossible to undo. Georghiou, ¶ 21. After a launch, health insurance providers will be unlikely to cover prescriptions for SENSIPAR® without significant bargaining and permanent concessions from Amgen. Hausman, ¶¶ 9-13, 24, 32. These third-party payers have significant influence over the pricing and reimbursement of prescription drugs, Hausman, ¶ 13, and SENSIPAR® is currently a preferred "Tier 1" drug for most insurers. Georghiou, ¶ 20. Now that Piramal has launched, however, SENSIPAR® could plummet to "Tier 3" status, resulting in larger patient copays and leading prescribing physicians to try less expensive treatments first. Georghiou, ¶¶ 20, 24. Moreover, many states *require* generic drug substitution absent explicit instructions from the physician—something physicians are unlikely to do. Georghiou, ¶¶ 18-20.

The Medicare reimbursement policy that presently governs the administration of SENSIPAR®, the "Transitional Drug Add-on Payment Adjustment" policy (TDAPA), could further accelerate Amgen's market share losses. Under TDAPA, until at least January 2020,

EXHIBIT 27

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **NOTICE OF MOTION AND MOTION BY AMGEN FOR A PRELIMINARY INJUNCTION** Date: March 2, 2015 Time: 1:30 PM Location: Courtroom 3, 17th Floor

1. Irreparable Harm to Research and Development

Amgen—unlike Sandoz—is an innovator. It invests substantially to develop novel, potentially life-saving products through primary research and development. Revenue for that research comes from Amgen's commercial products, including Neupogen® and Neulasta®. That research will be immediately and irreversibly harmed if Sandoz's biosimilar filgrastim draws sales from Amgen's products. *See* Philipson Report ¶¶ 20-59, 83-101. The missed opportunities in research or development of a product could not be remedied later by an injunction or an award of damages. In addition, Sandoz's entry into the market could cause Amgen to have to lay off the highly skilled research and development scientists whose projects would now go unfunded. This is irreparable harm: "[D]amage caused by a loss in personnel and the impact this would have on [a] company are indeed significant and unquantifiable." *AstraZeneca LP* v. *Apotex, Inc.*, 623 F. Supp. 2d 579, 612 (D.N.J. 2009), *supplemented*, 623 F. Supp. 2d 615 (D.N.J. 2009) and *aff'd*, 633 F.3d 1042 (Fed. Cir. 2010).

In the preliminary injunction context, the law must guard against that outcome. In *Bio-Technology Gen. Corp.* v. *Genentech, Inc.*, the Federal Circuit affirmed the finding of irreparable harm based in part on Genentech's being "required to reduce its research and development activities" and because of the loss of revenue that would occur absent an injunction. 80 F.3d 1553, 1566 (Fed. Cir. 1996). Another court noted that "a significant disruption or loss of research that otherwise would have been sponsored or completed by [plaintiff] as well as a scaling back of investment in research and development which otherwise would not have occurred" are losses that cannot be "adequately compensated by a monetary payment." *Eli Lilly & Co.* v. *Teva Pharm. USA, Inc.*, 609 F. Supp. 2d 786, 812 (S.D. Ind. 2009). Irreparable harm has also been found in the context of a permanent injunction when "a reduction of revenue would subsequently impact [a pharmaceutical company's] ability to allocate its resources to product development." *Pozen Inc.* v. *Par Pharm., Inc.*, 800 F. Supp. 2d 789, 824 (E.D. Tex. 2011) *aff'd*, 696 F.3d 1151 (Fed. Cir. 2012).

EXHIBIT 28

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EXHIBIT 29

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EXHIBIT 30

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EXHIBIT 31

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