IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

OSI PHARMACEUTICALS, INC., PFIZER, INC., and GENENTECH INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 09-185-SLR
MYLAN PHARMACEUTICALS INC.,	)	
Defendant.	)	

Jack B. Blumenfeld, Esquire and Maryellen Noreika, Esquire of Morris, Nichols, Arsht & Tunnell LLP. Counsel for Plaintiffs. Of Counsel: Leora Ben-Ami, Esquire, Benjamin Hsing, Esquire, Daniel Bogliogi, Esquire and Sapna W. Palla, Esquire of Kaye Scholer LLP.

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OPINION

Dated: May 1, 2012
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Applications ("ANDAs") by Mylan Pharmaceuticals Inc. ("Mylan") and Teva Pharmaceuticals USA, Inc. ("Teva") seeking to market generic versions of Tarceva® (erlotinib tablets), used to treat certain indications of non-small cell lung cancer and pancreatic cancer. Plaintiff OSI Pharmaceuticals, Inc. ("OSI") is the holder of approved New Drug Application ("NDA") No. 021743 for Tarceva®. OSI and plaintiff Pfizer, Inc. ("Pfizer") are owners of U.S. Patent Nos. 5,747,498 ("the '498 patent"), 6,900,221 ("the '221 patent") and 7,087,613 ("the '613 patent"). Plaintiff Genentech Inc. ("Genentech") is a "co-exclusive licensee" of these patents, which are listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book")[1] for Tarceva®. (D.I. 54 at ¶¶ 14, 19, 21) In December 2009, the '498 patent was reissued as U.S. Reissue Patent No. RE 41,065 ("the RE '065 patent"), which has been added to the Orange Book for Tarceva®.

In February 2009, OSI and Pfizer received a letter from Teva notifying them that Teva had filed ANDA No. 91-059 with a Paragraph IV certification[2] alleging that the '498, '221 and '613 patents are invalid, unenforceable, and/or not infringed by Teva's generic erlotinib hydrochloride tablets. (*Id.* at ¶ 26) Shortly thereafter, also in February 2009, Mylan sent notice to OSI and Genentech that Mylan filed ANDA No. 91-002 with a

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[1]The Orange Book must list "each drug which has been approved for safety and effectiveness through an NDA." *See* 21 U.S.C. §§ 355(j)(A)(ii).

[2]*See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

Paragraph IV certification alleging that the '498, '221 and '613 patents are invalid, unenforceable, and/or not infringed by Mylan's generic erlotinib hydrochloride tablets. (*Id.* at ¶ 31) On March 19, 2009, plaintiffs filed Civ. Nos. 09-185 and 09-186, alleging infringement of the '498, '221 and '613 patents by Teva and Mylan, respectively.[3] The cases were consolidated. In January 2010, after the issuance of the RE '065 patent, plaintiffs filed an amended and supplemental consolidated complaint in Civ. No. 09-185, alleging infringement of the RE '065, 221 and '613 patents by Teva and Mylan. (*Id.*) Teva and Mylan brought counterclaims for noninfringement and for invalidity. (D.I. 56, 57)

After the close of fact discovery, Teva moved to amend its pleadings to add the defenses of invalidity based on obviousness-type double-patenting; the court denied the motion. (D.I. 172, 213) A pretrial conference was held March 3, 2011. Teva and Mylan conceded infringement of claims 1, 2, 4, 8, 34 and 35 of the RE '065 patent and claim 53 of the '221 patent. (D.I. 198 at 2) On March 11, 2011, the court denied Teva's motion for reconsideration of the court's denial of its motion to amend. (D.I. 218) A settlement was reached between plaintiffs and Teva on the eve of trial. (D.I. 222, 223) Mylan presented its invalidity defenses during a five-day bench trial commencing March 14, 2011. On June 30, 2011, the court entered an order enjoining Mylan from launching its generic product until the court's decision issued. (D.I. 231) The validity issues have been fully briefed post-trial. (D.I. 232, 233, 234) The parties represent that the 30-

[3] *See* 35 U.S.C. § 271(e)(2)(A) ("(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]").

month statutory stay expires "on or about May 18, 2012."[4] (D.I. 232 at 1; D.I. 233 at 3)

The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. EGFR and NSCLC

1. A discussion of the technology at issue is best framed by an overview of epidermal growth factor receptor ("EGFR") and its role vis-a-vis cancer cells. EGFR is a receptor tyrosine kinase that is involved in transmitting signals from the outside of a cell to the inside of a cell. In normal cells, epidermal growth factor (or "EGF") binds to EGFR, which will cause a second EGFR or one of its family members together to bind to it, resulting in the transfer of a phosphate to the EGFR. This phosphorylation "initiates a cascade of signalling events within the cell, leading to increased survival and increased cell proliferation[.]" (D.I. 226 at 466:14-467:2) A EGFR tyrosine kinase inhibitor is a small molecule that penetrates a cell, binds to the catalytic portion of the kinase, and inhibits its enzymatic activity in transferring a phosphate. (*Id.* at 467:5-8) There are also EGFR kinase inhibitors that are not tyrosine kinase inhibitors, such as monoclonal antibodies that bind to EGFR, that are not the subject of the patents in suit. (*Id.* at 467:18-23)

2. Receptor tyrosine kineases are "frequently aberrantly expressed in common

[4] *See* 21 U.S.C. § 355(j)(5)(B)(iii).

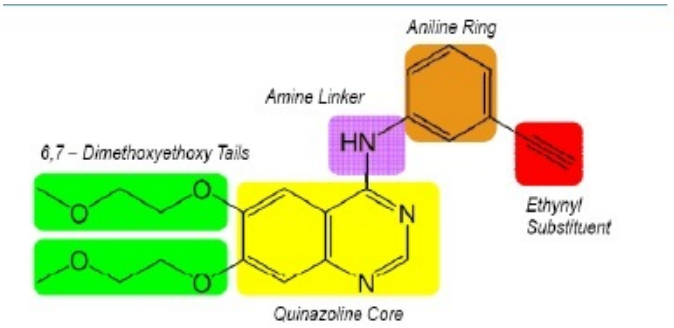
human cancers," and "[i]t has also been shown that epidermal growth factor receptor (EGFR) which possesses tyrosine kinase activity is mutated and/or overexpressed in many human cancers[.]" (RE '065, col. 1:24-48)

3. There are two general types of lung cancer: non-small cell lung cancer ("NSCLC"), making up 80-85% of cases, and small-cell lung cancer ("SCLC"), which is about 10-15% of all lung cancers. (D.I. 227 at 806:18-24 (85%/15% ratio); DTX-365 at 365 (80% of lung cancers classified as NSCLC, and 10% have both small-cell and non-small cell elements)) NSCLC is further divided into three types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. (D.I. 224 at 70:17-24) Doctors' classification of the cancer is important because NSCLC and SCLC have "distinct morphology, genetics, biology and clinical behavior." (DTX-433 at 310)

2. Erlotinib

4. Erlotinib, or N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (formula $C_{22}H_{23}N_3O_4$), is a kinase inhibitor.[5] The structure of erlotinib is below, highlighted to differentiate the molecule's functional segments: the quinalone core (yellow); an anilino group comprised of the amine linker (purple); an analine ring (orange); 3'-position substitution with an ethynyl substituent (red); and substitution at the 6,7-potisions with dimethoxyethoxy tails (green).

[5] *See gen.* PubChem, *erlotinib - Compound summary*, available at http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=176870&loc=ec_rcs.

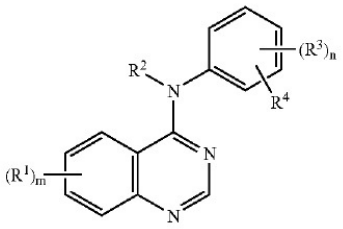


(D.I. 233 at 4-5) Tarceva® contains erlotinib as the hydrochloride salt.

3. '498 and RE '065 patents

5. The '498 patent was filed May 28, 1996 and issued May 5, 1998; it claims priority (as a continuation-in-part) to a PCT application filed June 6, 1995. The RE '065 patent was issued on December 29, 2009, from a reissue patent application filed February 27, 2008. The patents, entitled "Alkynl and Azido-substituted 4-Anilinoquinazolines," list Rodney Caughren Schnur and Lee Daniel Arnold as inventors, and are assigned to OSI and Pfizer. As a reissue patent, the RE '065 patent has an identical specification to the '498 patent.

6. The disclosed invention relates to compounds of the formula I -



and to pharmaceutically acceptable salts thereof, which compounds are useful for

treating hyperproliferative diseases, such as cancer. The “R” groups and “n” and “m” values are defined in the specification. The invention also relates to processes of making the compounds of formula I and to methods of using them in the treatment of disease. (RE ‘065 patent, abstract) The specification recites many preferred compounds according to the invention by chemical nomenclature, which for brevity’s sake, will not be reiterated here. Erlotinib is identified as one of the specifically-preferred compounds. (*Id.*, col. 4:15-16)

7. As background, the patents provide that 4-(substituted phenylamino) quinazoline derivatives are useful in the treatment of cancers in mammals. (RE ‘065 patent, col. 1:13-15) More specifically,

> it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor[,] selectively attenuates the growth in athymic nude mice of transplanted human mammary carcinoma which expresses epidermal growth factor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma which does not express the EGF receptor.

(*Id.*, col. 1:49-57) The compounds of the invention are the result of the continued search for improved anti-cancer pharmaceuticals. (*Id.*, col. 2:1-4)

8. While more specific methods are also disclosed, the specification generally provides that the formula I compounds and pharmaceutically acceptable salts thereof can be prepared “by any process known to be applicable to the preparation of chemically-related compounds,” and “may be made from the appropriately substituted quinazoline using the appropriately substituted amine.” (*Id.*, col. 8:50-56) Similarly, while specific administrative methods are discussed, the “[a]dministration of the active compounds [generally] can be effected by any method which enables delivery of the

compounds to the site of action (e.g., cancer cells)," which methods include "oral routes, intraduedenal routes, parenteral injection . . ., topical administration" and others. (*Id.*, col. 15:39-45)

9. It is disclosed that the active compounds of the invention are potent inhibitors of EGFR and may be used on a "variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors)," as well as for possible activity against "a range of leukemias and lymphoid malignancies" and "inflammatory, angiogenic and immunologic disorders." (*Id.*, col. 13:60-col.14:23) A procedure for determining the "in vitro activity of the active compounds in inhibiting the receptor tyrosine kinase (and subsequent proliferative response, e.g., cancer)" is provided. (*Id.*, col. 14:23-26 et seq.) The inventors state that, "[a]lthough the inhibitory properties of the compounds of [f]ormula I vary with structural change as expected, the activity generally exhibited by these agents, determined in the manner described above, is in the range of IC_{50} = 0.001-30 μM." (*Id.*, col. 14:66-col. 15:2) This IC_{50}[6] value is the only information that the inventors provide as to the properties of the disclosed compounds; no *in vivo*, pharmacokinetic or pharmacodynamic data is described. (D.I. 225 at 286:19-287:2; D.I. 226, 546:8-14)

10. Claim 1 was consistent from the '498 to the RE '065 patent, claiming a compound of formula I, further defining m, R^1, R^2 and n. Claim 8 of the '498 patent was originally a Markush-style claim, listing specific permeations of the compound of claim 1.

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[6]Generally, IC_{50} (or the half maximal inhibitory concentration) is a measure of the effectiveness of a compound in inhibiting a biochemical action.

As reissued, claim 8 in the RE ‘065 patent now claims only erlotinib. The ‘498 patent contained claims specifically directed to the use of the compound of formula I in the treatment of cancer. As reissued, the RE ‘065 patent contains claims directed to the treatment of psoriasis.

11. In summary, plaintiffs have alleged, and Mylan has stipulated to, infringement of claims 1, 2, 4, 8, 34, and 35 of the RE ‘065 patent. Claims 1, 2, and 4 generically cover erlotinib, and claim 8 is specific for the compound erlotinib. Claims 34 and 35 further specify that erlotinib is in the form of, respectively, a pharmaceutically acceptable salt or a hydrochloride salt.

4. ‘221 patent

12. The ‘221 patent, entitled “Stable Polymorph on N-(3-ethynylphenyl)-6,7-bis(2methoxyethoxy)-4-quinazolinamine hydrochloride, Methods of Production, and Pharmaceutical Uses Thereof,” was filed on November 9, 2000 and issued May 31, 2005. Priority is claimed to a provisional application filed November 11, 1999. There are nine listed inventors: Timothy Norris; Jeffrey W. Raggon; Richard D. Connell, James D. Moyer; Michael J. Morin; Barbara A. Foster; Karen J. Ferrante; and Sandra L. Silberman. The assignee is OSI.

13. The ‘221 patent relates to a stable form of erlotinib hydrochloride “designated the B polymorph, its production in essentially pure form, and its use,” as well as pharmaceutical compositions containing the stable polymorph B form, and to methods of treating hyperproliferative disorders (such as cancer) by administering the compound. (‘221 patent, abstract) The specification of the ‘221 patent incorporates the ‘498 patent in its entirety for its disclosure of erlotinib hydrochloride as an inhibitor of

EGFR. Also incorporated in its entirety is PCT International Publication No. WO 99/55683 for its disclosure of the mesylate form of erlotinib hydrochloride. (*Id.*, col. 1:27-62) The novel polymorphs of the '221 patent are described as having X-ray power diffraction patterns having particular characteristic peaks. (*Id.*, col. 2:27-col.3:3; fig. 3)

14. Plaintiffs have asserted, and Mylan has stipulated to, infringement of claim 53 of the '221 patent. Claim 53 depends from claim 44, which claims as follows:

> 44. A method for the treatment of NSCLC (non-small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HFV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.

Claim 53 depends from claim 44 and requires that the method be for the treatment of NSCLC. The specification provides that,

> [i]n the method, the therapeutically effective amount may be from about 0.001 to about 100 mg/kg/day, or from about 25 to about 200 mg/day. In the method, the therapeutically effective amount may also be from about 1 to about 7000 mg/day; from about 5 to about 2500 mg/day; or from about 25 to about 200 mg/day.

(*Id*., col. 4:31-37)

B. The RE '065 Patent: Obviousness

Insofar as the parties did not present any claim construction disputes requiring resolution (D.I. 189), the court proceeds to evaluate Mylan's first argument for invalidity: that claims 1, 2, 4, 8, 34, and 35 of the RE '065 patent are invalid as obvious in view of the prior art.

1. Obviousness standards

15. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

16. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id*. at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id*. at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id*. at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry

out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

17. A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* Federal Circuit precedent has also established that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds," and that particular types of structural similarity can give rise to a case of prima facie obviousness. *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1312 (Fed. Cir. 2011) (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

18. A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, --- F.3d ---, 2012 WL 1320225 (Fed. Cir. Apr. 16, 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

19. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

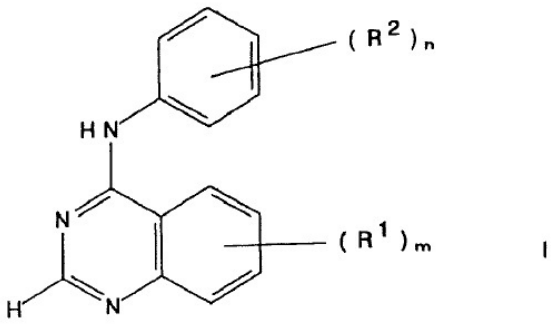
PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

2. Mylan's evidence

a. Overview

20. Mylan has identified a prior art compound differing from erlotinib only in that it contains an ethynyl group, rather than erlotinib's methyl group, at the 3'-position. The disclosure of this compound is at example 51 of Zeneca's European Patent Application No. 0 566 226 A1, naming Andrew John Barker as inventor, filed January 15, 1993 (hereinafter, the "Barker '226 application"). (DTX-286) The Barker '226 application related to "quinazoline derivatives, or pharmaceutically acceptable salts thereof, which possess anti-cancer activity," as well as their methods of manufacture, pharmaceutical compositions containing them, and the compounds' use in mammals. (*Id.* at p.2:1-5) The inventor stated that "it has been indicated [in the literature] that receptor tyrosine kinease inhibitors will prove to be useful in the treatment of a variety of human cancers"

and, while "[m]any quinazoline detivatives are already known," it has now been discovered that certain quinazoline derivatives possess anti-cancer properties. (*Id.* at p.2:32-49) The invention provides a quinazoline derivative of the formula –



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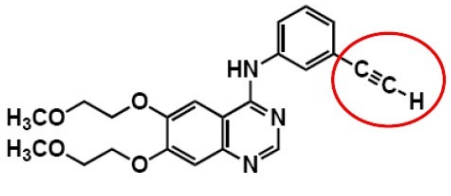
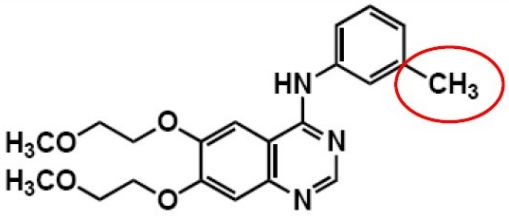
providing specific alternatives for the values m, n, R^1 and R^2. (*Id.* at p.1, 59 (claim 1))

21. Among the invention's non-limiting examples, the following disclosure was provided for example 51.

Example 51

2-Bromoethyl methyl ether (0.834 g) was added to a stirred mixture of 6,7-dihydroxy-4-(3'-methylanilino)quinazoline (0.534 g), potassium carbonate (0.828 g) and DMA (10 ml). The mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. The gum so obtained was dissolved in ethyl acetate (4 ml) and acidified by the addition of a saturated solution of hydrogen chloride in diethyl ether. The precipitate was isolated. There was thus obtained 6,7-di-(2-methoxyethoxy)-4-(3'-methylanilino)quinazoline hydrochloride (0.292 g), m.p. 218-220°C.
NMR Spectrum: (CD_3SOCD_3) 2.34 (s, 3H), 3.36 (s, 6H), 3.75-3.8 (m, 4H), 4.1-4.5 (m, 4H), 7.14 (d, 1H), 7.37 (t, 1H), 7.40 (s, 1H), 7.48 (m, 2H), 8.35 (s, 1H), 8.79 (s, 1H);
Elemental Analysis: Found C, 59.8; H, 6.4; N, 9.9;
$C_{21}H_{25}N_3O_4$. 1HCl requires C, 60.0; H, 6.2; N, 10.0%.

(DTX-286 at 46) There is only one difference between this compound (6,7-di-(2-methoxyethoxy)-4-(3'-methylanilino)quinazoline) and erlotinib: erlotinib bas an ethynyl group (HC≡C–) at the 3' position of the molecule, while the compound of example 51 has a methyl group (H_3C–) at the 3' position, as highlighted below.

Erlotinib	*Example 51 of Zeneca (Barker) '226 Application*
	

(D.I. 232 at 12)

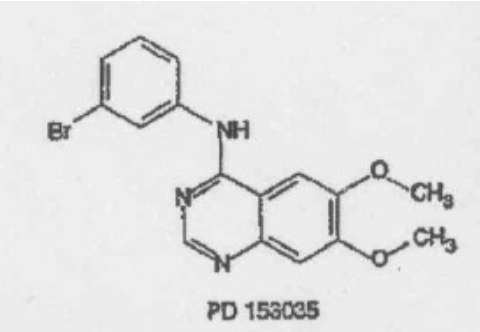
22. Mylan argues that, "given a medicinal chemist's knowledge of the chemical similarities between methyl and ethynyl, and the specific suggestion in the [prior art] to use a 'small, non-polar group' at that position, clear and convincing evidence establishes that it would have been obvious for a medicinal chemist, working on new EGFR inhibitors, to start with the compounds of [the Barker] '226 application and make erlotinib." (D.I. 232 at 30) More specifically, it is Mylan's contention that the ordinary medicinal chemist would have: (1) started with the Barker '226 application; (2) identified the gap in the claim coverage as not covering alkynyl (such as ethynyl) and alkenyl; (3) recognized a suggestion in the prior art to use a small, non-polar group, such as ethynyl, at the 3'-position; and (4) filled the gap by putting an ethynyl group at the 3'-position of the best compounds of the Barker '226 application. "This approach would have satisfied the medicinal chemist's motivation to make EGFR inhibitors other than those expressly claimed in [the Barker] '226 application." (*Id.* at 32)

b. Selection of example 51 as a starting compound

23. As noted above, the earliest priority date for the RE '065 patent is June 6, 1995. Mylan argues that, at the time of the invention, the 4-anilinoquinazolines (or "4-

AQs") of the Barker '226 application were the best starting point for making an EGFR inhibitor. (D.I. 232 at 32) Mylan's expert, Dr. Clayton Heathcock ("Heathcock"), Emeritus Professor of Chemistry from the University of California at Berkeley, testified regarding several review articles following the publication of the Barker '226 application (in 1993) indicating that quinazolines were ideal in this regard. (D.I. 225 at 298:16-300:19) A March/April 1993 publication in "The Current Opinion in Therapeutic Patents," for example, discussed the benefits of quinazoline derivatives as receptor tyrosine kinase inhibitors, and disclosed preferred compounds including 4-(3'-methoxyanilino)quinazoline. (DTX-428) Another example is a June 1994 article by David Fry ("Fry"), a Parke-Davis scientist, entitled "Expert Opinion on Investigational Drugs" (hereinafter, the "Fry review article"). (DTX-354; D.I. 225 at 303:7-304:1) The Fry review article discussed epidermal growth factor receptor kinase as a target for cancer chemotherapy. (DTX-354) According to Heathcock, a person of ordinary skill in the art would have noticed the statements in the Fry review article that certain 4-AQs were the most potent inhibitors of the tyrosine kinase thus far to be revealed, and that Parke-Davis was currently working in this area. (D.I. 225 at 304:5-21)

24. Fry subsequently published an article entitled "A Specific Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase" in the high-profile journal S*cience* in August 1994 (hereinafter, the "Fry *Science* article"). (PTX-43; D.I. 225 at 301:10-15) The Fry *Science* article disclosed a molecule called "PD 153035," as labeled by Parke-Davis Pharmaceutical Research, having the following structure.



(PTX-43 at fig. 1) Heathcock testified that this compound is the same as that in example 2 of the Barker '226 application, and that the Fry *Science* article indicated that it is both a very potent compound and is highly selective for EGFR. (D.I. 225 at 301:2-303:6) Mylan argues that "[i]n view of the Fry *Science* article, [ ] Fry's review article, and other valuable information, there was little, if any, doubt that the 4-AQs were the best place for a medicinal chemist to start making potent, selective EGFR inhibitors." (D.I. 232 at 11)

25. To this end, Mylan also argues that the Barker '226 application suggests compounds that were better EGFR inhibitors than others. Only thirteen specific compounds were claimed in the Barker '226 application; these thirteen compounds were disclosed in the specification among a list of 32 "specific preferred" compounds.[7] (D.I. 232 at 11; DTX-286 at 18, 58-62 (claims 7, 9); D.I. 225 at 311:21-312:5) The compound of example 51 was one of three compounds claimed in claim 9. (D.I. 225 at 311:10-14) The Barker '226 application did not disclose biological data for the compound of example 51. (*Id.* at 313:1-3) Biological data was only disclosed for five 4-

[7]Still additional compounds were listed as "preferred" rather than "specific preferred" compounds according to the specification.

AQ compounds.[8] (DTX-286 at 21) Heathcock explained that this disclosure is

> sufficient to show the reader that this whole class of compounds is good . . . [T]hey've selected examples [for which biological data was provided] with a variety of different substituents, and so that [ ] is the important message a medicinal chemist would take from this set of data. It would not at all be presumed to be all the biological data they had. You would naturally assume that they had tested a lot more than just five[9] compounds. And there was no reason to think that they had picked out their best five compounds to illustrate with biological data. For one thing, I think none of these five compounds were listed in the claims, and at least three of them were not even called specific preferred compounds of the invention. I would take this, and I think a person of ordinary skill in the art would take this data to be representative of the family.

(D.I. 225 at 409:9-410:5)

26. Heathcock also testified that, of the 105 compounds actually made, between 75 and 80 examples had a methyl (alkyl) group at the 3' position of the molecule, "and a fairly large number, 15 or so, had a halogen or some other substituent at the 3' position." (*Id.* at 310:7-18) It is his opinion, therefore, that "medicinal chemists would notice that alkenes and alkynes were omitted right after alkyl [groups] in [the specification's] definitions," and "would take the other clues from the [Barker] '226 [application] to decide, well, if I'm going to put . . . an alkene and alkyne in this. . . aniline position, what should I use for the quinazoline?" (*Id.* at 310:23-311:4) Looking at the Barker '226 application to determine what the inventors regarded as the best, a medicinal chemist would "swap out whatever [he] had in the aniline ring and put in an

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[8]"[B]y way of example," IC50 data was provided for three tests on: 6,7-dimethoxy-4(3'-methylanilino)quinazoline; 6,7-dimethoxy-4-(3'-triflouromethylanilino)quinazoline; 6-acetamido-4-(3'-methylanilino)quinazoline; and 7-(2-hydroxyethoxy)-6-methoxy-4-(3'-methylanilino)quinazoline. (DTX-286 at 21:23-30)

[9]It is unclear why Heathcock refers to five compounds. As noted previously, Mylan asserts in its post-trial papers that there were only four exemplified; the court has also identified four compounds on the cited page of the Barker '226 application.

aniline that had this alkynyl group or the alkenyl." (*Id.* at 31144-9)

27. The debated substituent (on the aniline ring) is the R_2 position. The Barker '226 application provides that the R^2 group may be hydrogen, hydroxy, halogeno, triflouromethyl, amino, nitro, cyano, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkylthio, (1-4C)alkylsulphinyl or (1-4C)alkylsulphonyl."[10] (DTX-286 at 3:50-52, 4:30-32, 4:46-51) Claim 1 also requires that each R^2 is one of these groups. (*Id.* at 59:49-51) The specification provides suitable values for R^2 in various combinations, for example, "[a] suitable value for R^1 or R^2 when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl[.]" (*Id.* at 5:11-13) In sum, the Barker '226 application names alkyl groups for R^2 – the relevant radical of an alkane, or a hydrocarbon substituent having only single bonds. As Heathcock explained, however, the specification stops short of naming alkene (a hydrocarbon substituent having a carbon to carbon double bond) or alkynes (a hydrocarbon substituent having a triple bond between two carbon atoms) for the R^2 position. Ethynyl (HC≡C-), the substituent in erlotinib corresponding to the R^2 position in the Barker '226 application, is an alkynyl group. (D.I. 226 at 405:20-21)

28. Mylan refers to the foregoing as a "gap" in the coverage of the Barker '226 application. According to Heathcock, "if you are trained as an organic chemist, which a medicinal chemist would be, in many cases . . . you're going to do a double-take, because right after alkyl, something could be there that isn't[:] alkenyl and alkynyl[,]" despite the inclusion of other more complicated substituents. "[T]hat would be

[10](1-4C) means that you can have one, two, three or four carbon atoms in the functional group. (D.I. 227 at 723:2-4)

recognized as an opening in this patent." (D.I. 225 at 307:3-15) A person of skill in the art is going to look at references like the Barker '226 application "to figure out what makes it work so well," including the definitions. (*Id.* at 305:22-306:4) Heathcock explained that, because there are 32 lines of text detailing the possibilities for the R^1 position, but only two lines of definition for R^2 ("a much more manageable group to get your arms around"), "a medicinal chemist is going to look there [at R^2] first to see . . . what works there." (*Id.* at 306:12-22) It is at this point that a person of ordinary skill in the art (a medicinal chemist) would notice the absence of alkenyl and alkynyl groups as R^2 examples. (*Id.* at 306:23-307:15)

29. Mylan also argues that the similarity of the alkyl, alkenyl, and alkynyl groups supports an obviousness determination. As noted above, all three are hydrocarbons and have single-bonded, double-bonded, and triple-bonded carbons, respectively. Heathcock referred to the these hydrocarbons as the "three siblings" of the hydrocarbon family. (*Id.* at 308:4-19) Mylan points to two prior art articles classifying "methyl, ethyl or ethynyl" and "hydrogen, methyl, ethyl or ethynyl" groups as "small," and OSI's expert did not dispute this characterization. (DTX-572 at 6131; DTX-589 at 117; D.I. 227 at 722:4-14, 771:18-772:6)

30. Another similarity is that both ethynyl groups (erlotinib) and methyl groups (a common 3' substituent used in the 4-AQs in the Barker '226 application) are non-polar, thus, lipophilic. (D.I. 225 at 310:7-13, 322:12-14, 325:9-11, 328:3-9)

c. Motivation to modify example 51: the Barker Abstracts

31. As discussed previously, it is Mylan's position that, after starting with the Barker '226 application and identifying the gap in its claim coverage at the 3'-position, a

person of ordinary skill in the art would have been further motivated to fill the gap (with an ethynyl group) in view of: an abstract by A. J. Barker at al. entitled "Structure Activity Relationships of 4-anilinoquinazolines as Inhibitors of EGFR-Tyrosine Kinase Activity" (hereinafter, the "ESMO abstract");[11] and an abstract by the same authors entitled "Inhibition of EGF Receptor Tyrosine Kinase Activity by 4-anilinoquinazolines" (hereinafter, the "BJC abstract")[12] (collectively, the "Barker Abstracts"). (DTX-107; DTX-112; D.I. 232 at 14; D.I. 225 at 305:22-306:22)

32. The ESMO abstract disclosed a series of quinazolines having a variety of substituted anilines at the 4-position, and stated that "[t]he most potent inhibitors possess small, relatively non-polar substituents in the meta-position of the aniline ring[.]" (DTX-107) The small, non-polar group exemplified in the ESMO abstract was a "chloro group" (chlorine) at the 3'-position.[13] (D.I. 232 at 15) The BJC abstract similarly disclosed a new series of potent receptor tyrosine kinase activity bearing substituted anilines at the 4-position, and stated that "[t]he most potent [4-AQs] [IC_{50} ca. 20nM] have small non-polar meta substituents on the aniline ring[.]" (DTX-112) In view of the

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[11]Published in Annals of Oncology, the Official Journal of the European Society for Medical Oncology, at volume 5, supplement 5 (1994). (DTX-107) The exhibit indicates that the abstract was associated with the "8th NCI-EORTC Symposium on New Drugs in Cancer Therapy" from March 15-18, 1994 in Amsterdam, The Netherlands. (*Id.*) The precise date of publication is unclear.

[12]Published in the British Journal of Cancer, the Scientific Journal of the Cancer Research Campaign. (DTX-112) The exhibit indicates that the abstract was associated with the "BACR/ACP Annual Meeting" from March 27-30, 1994 in Birmingham, United Kinggdom. (*Id.*) The precise date of publication is unclear.

[13]Heathcock testified that a chloro group is non-polar and lipophilic. (D.I. 225 at 324:8-16)

Baker Abstracts, Mylan asserts that a person of ordinary skill in the art would have been motivated to make EGFR inhibitors using the best 4-AQs (as disclosed by the Barker '226 application) having the small, non-polar ethynyl group at the 3'-position . (D.I. 232 at 32) As Heathcock explained, the Barker abstracts provided "information not confined to necessarily what was presented in the [Barker '226 application]." (D.I. 225 at 385:1-4)

33. With respect to selection of an ethynyl group at the 3'-position, Heathcock states that an ethynyl group is small and non-polar, and "is certainly not contradicted by [the BJC] abstract." (*Id.* at 328:3-6) Heathcock testified that "small" is "kind of a relative term," however, "[i]n the context of this matter, small definitely means no more than a few carbons, two or three at most, and really there are a very small number of lipophilic substituents that are larger than that." (D.I. 225 at 402:3-9) Mylan also points to testimony by OSI's expert, William L. Jorgensen ("Jorgensen") (a professor at Yale University), that ethynyl is "small." (D.I. 232 at 26 (citing D.I. 227 at 780:9-11))

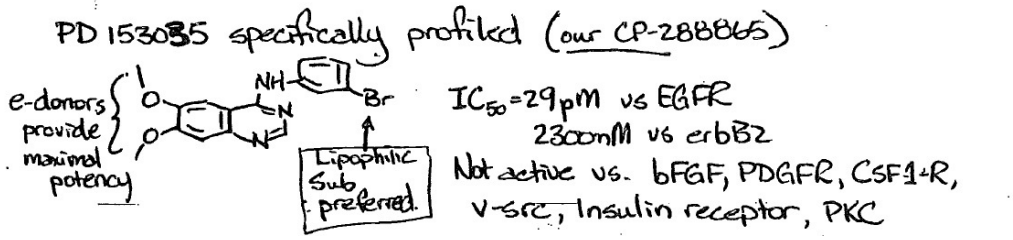
34. Mylan argues that the Barker '226 application was the "logical starting point:" "Once [a medicinal chemist] noticed that there is this omission in the definitions for the anilino ring, [he] would then fill that missing definition with the things that were missing, the ethynyl and the vinyl being the two smallest representatives of the multiple-bonded hydrocarbon type groups." (D.I. 232 at 17; D.I. 225 at 334:6-18) Mylan also highlights Jorgensen's testimony that a person of ordinary skill in the art would "use[ ] substituents that one feels are suitable for medicinal chemistry," and "could probe larger substituents" as "a normal medicinal chemistry activity." (D.I. 227 at 7801:17-781:6) When asked about probing smaller substituents, Jorgensen stated that "changing the

size of the **halogen**," for example, trying fluorine, chlorine, and bromine, is a "normal exercise." (*Id.*) (emphasis added) To summarize Mylan's contentions, recognizing an ethynyl group as a small, non-polar group similar to the methyl group used at R^2 in example 51 of the Barker '226 application, and having observed the "gap" in coverage at R^2 in contrasting the broader protection for the 6- and 7-positions of the quinazoline ring (R^1), a medicinal chemist would have found it easy to modify example 51 in this manner in order to avoid the claim coverage of the Barker '226 application. (D.I. 232 at 14; D.I. 225 at 305:22-306:22)

35. According to Mylan, Pfizer followed this exact path to arrive at erlotinib. Pfizer made its first 4-AQ with a 3'ethynyl group on April 12, 1994, "around the time that [the] Barker Abstracts suggested that small, non-polar groups are best for 4-AQs." (D.I. 232 at 21; D.I. 226 at 505:14-25) According to Dr. Lee Daniel Arnold ("Arnold"), the lead medicinal chemist on Pfizer's EGFR Project Team and co-inventor of the RE '065 patent, Pfizer and Zeneca were in a "competitive race to identify the best EGFR inhibitor" and had, on several occasions, identified the same lead molecules in their pursuits. (D.I. 226 at 490:11-21, 581:16-20) On June 28, 1994, Arnold relayed an abstract from a scientific conference held in Salt Lake City, Utah between June 21-25, 1994 to members of his team at Pfizer. (DTX-93) The abstract discussed the high potency of PD 153035, disclosed in the Fry *Science* article and as example 2 of the Barker '226 application, which was also known to Pfizer as "CP-288865." (*Id.*) Arnold's handwritten notes[14] state, with respect to the 3' bromine, that "lipophilic" substitutions

[14]The notes were based on information relayed to Arnold by Dr. John Lowe, a Pfizer chemist, at the conference. (DTX-93; D.I. 226 at 579:13-580:4)

are "preferred."



(DTX-93) "[A] few months later," in November 1994, Pfizer scientists used an ethynyl group at the 3'-position to make erlotinib. (D.I. 232 at 21; D.I. 226 at 464:12-15)

3. Analysis

a. Selection of the lead compound

36. It was not genuinely disputed that the Barker '226 application was "one of the best pieces of prior art." (D.I. 226 at 674:12-14) The parties agree that the compound of example 51 was one of thirteen preferred EGFR inhibitors disclosed in claims 7 and 9 therein. The fact that thirteen 4-AQ compounds were specifically claimed is not dispositive, however, of the lead compound issue. *See Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Rather,

> it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; [the court] must look at the state of the art **at the time the invention was made** to find a motivation to select and then modify a lead compound to arrive at the claimed invention. . . Potent and promising activity in the prior art trumps mere structural relationships.

Id. (citations omitted) (emphasis in original); *see also Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned

identification of a lead compound.").

37. Mylan's proffered explanation for why example 51 would have been selected from the thirteen compounds identified in claims 7 and 9 is that the Barker '226 application provides a specific method for preparing the hydrochloride salt of the compound of example 51. (D.I. 232 at 12) Heathcock testified that certain publications, for example, the Fry review article, talked about the benefits of 4-AQs. (*Id.* at 32 (citing D.I. 225 at 298:16-300:19)) Similarly, Heathcock testified that a 1992 patent to Zeneca (hereinafter, the Zeneca "'772 patent") "made an impact because it reported about three dozen [ ] compounds [ ] with enough in vitro biological data to show that there was very good potency across the board in this family of [4-AQ] compounds." (*Id*. at 32 (citing D.I. 225 at 294:6-295:6); DTX-772) Mylan also argues that the 4-AQs of the Barker '226 application were "attractive starting points" for making novel EGFR inhibitors because 4-AQs can be made by high-speed synthesis. (D.I. 232 at 33) Pfizer was researching 4-AQs and was aware of the Barker '226 application coverage. (*Id.* at 34; PTX-310; DTX-98)

38. Absent from the foregoing, however, is any indication in the prior art regarding "useful properties" or "[p]otent and promising activity" for the thirteen compounds of claims 7 and 9 of the Barker '226 application, let alone example 51 specifically. *See Daiichi*, 619 F.3d at 1354. Mylan admits that the Barker '226 application does not disclose any biological activity for these thirteen compounds. (D.I. 232 at 11; D.I. 225 at 350:13-351:8) Mylan does not point to "knowledge in the art of the functional activities and limitations" of the focused-on compounds. *See Daiichi*, 619 F.3d at 1354. Heathcock admitted that biological data is very important to medicinal

chemists. (D.I. 225 at 352:14-16) Mylan's theory boils down to a general assertion that a person of ordinary skill in the art would recognize that "there is something really that Zeneca likes about these 13 compounds or [it] wouldn't have taken the time to claim them individually by name [in the Barker '226 application]." (*Id.* at 335:19-22)

39. OSI presented the testimony of Dr. Alexander Bridges ("Bridges"), a Parke-Davis scientist who worked on finding new EGFR inhibitors and has a dozen patents in that area. Bridges testified that example 51 of the Barker '226 application would be **less** of a candidate as a lead compound due to the fact that "you don't know anything about it." (D.I. 226 at 622:13-23) OSI's other expert, Jorgensen, explained that there are ten compounds for which IC_{50} and phosphorylation data is disclosed between the Barker '226 application, the Zeneca '772 patent and the Fry *Science* article. A person of ordinary skill in the art would look at these ten compounds because of the "well-defined IC_{50}" and, particularly, an "extremely potent" molecule in the Fry *Science* article, based on the biological data disclosed. (D.I. 227 at 745:19-747:21) Bridges agreed that the Fry *Science* article compound disclosed a (3' bromo-anilinoquinazoline) compound with "quite extraordinary potency," and also explained that the Barker '226 application itself disclosed a very potent quinazoline (IC_{50} of 5 nm) having a methyl group (CH_3) at the 3'-position. (D.I. 226 at 623:8-11, 626:1-5) Heathcock agreed that "in vitro potency is what drives medicinal chemistry discovery at the first stage." (D.I. 225 at 386:20-387:1) Heathcock "focus[ed] on the biological data when [he] talked about the '772 patent" but, in the absence of data for the thirteen compounds in the Barker '226 application, asks the court to focus only on the patent claims. (*Id.* at 351:9-352:13)

40. Finally, as OSI points out, the prior art disclosed other compounds with favorable characteristics that were not 4-AQs. (D.I. 225 at 387:2-396:7) One such compound, an indolyl amino quinazoline compound,[15] was not considered by Heathcock despite having a 1 nm potency. (*Id.*; PTX-11 at 15:40-45) In perspective, this is a higher potency than any of the compounds listed in the Barker '226 application or Zeneca's '772 patent. (D.I. 225 at 390:18-24)

41. In short, a person of ordinary skill in the art had several alternatives to consider and, since potency drives the research, the court is not persuaded by Mylan's argument that the ease of synthesis (rather than promising activity) would have led an ordinary artisian to pursue the 4-AQs of the Barker '226 application or example 51[16] as a lead compound. *See Daiichi*, 619 F.3d at 1354 (collecting cases). The court found Bridges' testimony more persuasive than Heathcock's in this regard.

b. Motivation to modify

42. Even if the court were to credit the motivation to select example 51 as the lead compound, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm*

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[15]Specifically, 6,7-dimethoxy-4-(5-indolyamino)quinazoline, having an IC_{50} of 0.001 μm, which converts to 1 nm. (PTX-11 at 15:40-45; D.I. 225 at 390:6-8)

[16]Mylan's obviousness argument embraces all thirteen compounds. (D.I. 232 at 32) However, it is the court's understanding that only the compound of example 51 can be modified at the 3'-position with an ethynyl group to provide erlotinib. (*Id.* at 12) Mylan has not specified how the other twelve compounds relate to erlotinib. When addressing the motivation to modify, the court will hereinafter refer only to the compound of example 51.

Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007) (citation omitted); *accord Daiichi*, 619 F.3d at 1352. In this regard, Mylan's proffered motivation to modify the compound of example 51 of the Barker '226 application is twofold: (1) an ordinary artisan would have looked for holes in patent coverage, identifying an alkynyl "gap" in coverage; and (2) filled the gap with ethynyl based on the Barker Abstracts' suggestions to use small or non-polar groups at the 3'-position. (D.I. 232 at 32)

43. The Federal Circuit has stated that "the requisite motivation [to modify] can come from any number of sources and need not necessarily be explicit in the prior art." *Eisai*, 533 F.3d at 1357 (citing *Aventis Pharma Deutchland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)). While the obviousness inquiry is a flexible one, Mylan does not provide any caselaw indicating that the motivation to modify may be derived specifically from the desire to avoid the prior art. *KSR* does not appear to specifically preclude this scenario so long as it is proven, by clear and convincing evidence, that "design need or market pressure to solve a problem" and "a finite number of identified, predictable solutions" existed such that species within a gap in patent coverage provided "known options" within the technical grasp of the ordinary artisan. *KSR*, 550 U.S. at 421.

44. This is not that case, however. In support for its argument, Mylan emphasizes that Arnold (at Pfizer) commented upon and circulated a patent abstract to his colleagues. (D.I. 232 at 35 (citing D.I. 226 at 578:10-582:19, DTX-93)) But what Arnold did with respect to one abstract is not informative with respect to motivation of the hypothetical person of ordinary skill in the art. Moreover, the Barker '226 application omits not only alkynes as possible groups for R^2, but alkenes as well. Halogens are

also not mentioned, such as the chloro- group disclosed at the 3'-position in the Barker Abstracts. While the precise number of alternatives is not clear, on this record, the court does not find persuasive Mylan's argument that the **absence** of teaching the ethynyl substituent in the Barker '226 application would have suggested to an ordinary artisan to select it.

45. The court next evaluates whether a motivation to modify the compound of example 51 of the Barker '226 application is provided by the Barker Abstracts. As discussed previously, the only compound disclosed in either abstract was a compound substituted at the 3'-position with a chlorine – a halogen. As Bridges explained, chlorine is a polar substituent; the dipole moments[17] of a halogen-substituted benzene ring is approximately four times that of a methyl-substituted benzene ring. (D.I. 226 at 631:11-633:13; PTX-232) Heathcock's description of the bonds between chlorine and bromine (another halogen) with carbon as "polar bonds" is consistent with this evidence. (D.I. 225 at 325:16-25, 383:19-384:13)

46. The court also notes that the ESMO abstract is internally inconsistent: it states a preference for "small, relatively non-polar substituents" at the 3'-position, but exemplifies a compound having a chlorine (a polar) substituent. Thus, the motivation to use a "non-polar" substituent is diminished, in some capacity, by its concurrent teaching to use a chloro group. The court does not attempt to quantify this effect,[18] except to

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[17]A measure of the separation of the negative and positive charges (polarity). (D.I. 226 at 631:7-8)

[18]Jorgensen testified that a person of ordinary skill in the art reading the ESMO abstract would have been "slightly confused" by the chloro group because the abstract says "nonpolar;" it is "sloppy" wording. (D.I. 227 at 713:2-14)

note that it does not find convincing Heathcock's testimony that "the chlorine itself **as it affects the properties of the molecule** is a non-polar substituent because adding the chlorine makes the **molecule** more lipophilic" and, thus, chlorine is akin to other lipophilic groups such as ethynyl. (D.I. 232 at 17; D.I. 225 at 324:6-325:15, 326:1-3) (emphasis added) First, both abstracts specifically stated that the 3' "substituent" must be non-polar.[19] Secondly, neither Barker Abstract discussed lipophilicity. The court found persuasive Bridges and Jorgensen's testimony that polarity and lipophilicity are different concepts involving different measures. (D.I. 226 at 629:13-635:7; D.I. 227 at 710:16-712:11, 714:16-719:12; PTX-232)

47. The experts agreed that an ethynyl group is a "small" substituent, as it has two carbon atoms. Mylan argues that, in view of the Barker Abstracts, "the most logical starting point for replacing the group at the 3' position of Barker's 4-AQs with an alkenyl group would have been to use the smallest such groups, namely, the ethenyl and ethynyl groups." (D.I. 232 at 17; D.I. 225 at 334:6-18) There are two flaws in this logic. Mylan concurrently asserts that the ESMO abstract's use of chlorine should be informative with respect to the size of the molecule, not with respect to the type of substituent (a halogen). Notwithstanding, Mylan's position presupposes that a skilled artisan would be seeking to replace the 3' substituent with an alkenyl group. As Jorgensen testified, there are 80 (lipophilic and non-lipophilic) alkyl substituents having

[19]As Jorgensen testified, a "substituent is something that is attached to another entity;" it is not the entire molecule. (D.I. 227 at 712:14-15)

one to four carbon atoms and that fit the general description for a "small" substituent.[20] (D.I. 227 at 720:15-723:11) Mylan's did not offer any credible evidence regarding why a skilled artisan would hone in on an alkenyl group.

c. Expectation of success

48. The court notes at this juncture that, even had Mylan proven that the ethynyl substituent was one of a "finite number of identified, predictable solutions," its evidence of its "anticipated success" is not clear and convincing. *KSR*, 550 U.S. at 421. Mylan concentrates on two documents in this regard. The first is an internal Pfizer memo (to the "EGFR Project Team" dated October 6, 1995), stating that "two newer acetylenic anilino inhibitors were highly selective **as expected**." (DTX-18) (emphasis added) Similarly, another Pfizer memo regarding "selectivity studies on CP-358774" (dated January 5, 1995) stated that the CP-358774 compound is "a potent and highly selective EGFR inhibitor, **as expected**." (DTX-19) (emphasis added) According to Mylan,

> [t]hese statements are not, of course, comparisons of erlotinib with the closest prior art. But the statements suggest that even Pfizer's own scientists expected erlotibin to be a selective EGFR inhibitor. Indeed, erlotinib's EGFR inhibitory activity aligns with the disclosures in Zeneca's Barker Abstracts, which taught that the most potent 4-AQ inhibitors had small non-polar groups (such as the ethynyl group) at the 3'-position.

(D.I. 232 at 40)

[20]The court makes no express finding regarding the conflicting testimony on the meaning of "small" as used in the Barker Abstracts in view of Mylan's lack of evidence indicating a finite universe of alternatives. *See In re Cyclobenzaprine*, --- F.3d ---, 2012 WL 1320225 at *8 ("Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious to try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed' and that skilled artisans would have had a reason to select the route that precluded the claimed invention") (citation omitted).

49. As an initial matter, the views of particular Pfizer researchers may not be indicative of those of the hypothetical person of ordinary skill in the art; Mylan offers no expert testimony in this regard. (*Id.*) Additionally, OSI presented credible evidence indicating that the prior art taught away from using ethynyl compounds because they "tended to be toxic" and "led to inactivation of critical [cytochrome P450] liver enzymes," except when used in very low dosages in birth control medications. (D.I. 226 at 506:19-507:12 ("at many other companies within the pharmaceutical industry, this type of substituent was forbidden"), 661:12-662:9; D.I. 227 at 724:2-16 ("[m]edicinal chemists have avoided ethynyl groups" and still do), 733:21-736:22 (ethynyl substituent is called a "suicide inhibitor" based on its affect on cytochrome p450 enzyme), 738:22-740:22; PTX-75 at 5582, 5584; PTX-427 at 147; PTX-103 at 484)

d. Secondary considerations

50. Finally, in formulating its decision, the court considered OSI's proffered evidence of nonobviousness.[21] OSI's first argument is that erlotinib has unexpectedly superior potency compared to the closest prior art, which is not example 51 of the Barker '226 application, but a 3'-ethyl compound disclosed in 2008 (which, it argues, falls within the claims of the Barker '226 application). (D.I. 233 at 42; PTX-230[22]) There is "no requirement that an invention's properties and advantages were fully known

[21]The court reads *In re Cyclobenzaprine*, *supra*, as requiring a review of such evidence even where it is clear that defendants can not meet their burden to prove obviousness by clear and convincing evidence.

[22]Defendants objected to the admission of PTX-230, a document depicting the 3'ethyl analog as well as its potency, on the basis that it was not prior art to the RE '065 patent.

before the patent application was filed." *Knoll Pharma. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 1381, 1385 (Fed. Cir. 2004). However, the court must assess secondary considerations against the background of the differences between the **prior art** and the claims at issue. *See Graham*, 383 U.S. at 17. OSI does not argue that the 3'-ethyl compound was actually disclosed in the prior art, and its synthesis and assessment 13 years after the priority date is not persuasive on this factor.

51. OSI also presented testimony by Dr. Malcom Moore ("Moore"), the head of the Division of Medical Onclogy at Princess Margaret Hospital in Toronto and the University Director of Medical Oncology at the University of Toronto. Moore testified that erlotinib is one of only two FDA-approved drugs to treat pancreatic cancer, which has the poorest 5-year survival rate for all cancers. (D.I. 227 at 902:22-904:12) Erlotinib is approved to be used in connection with the first drug, gemcitabine, a traditional chemotherapy drug. (*Id.*) Moore was the principal investigator of the Phase III trials for erlotinib with gemcitabine, which revealed a "stastically significant improvement in survival." (*Id.* at 907:3-12, 915:24-916:11, 907:22-908:3; PTX-81) Moore called the positive results "definitely unexpected" because treating pancreatic cancer has been "littered with failure in Phase III" and, thus, "any positive result in this disease is unexpected."[23] (*Id.* at 909:19-910:5)

52. As Mylan points out, Moore is not a medicinal chemist. "[A] witness not qualified in the pertinent art may not testify as an expert on obviousness or any of the

[23]While Mylan emphasizes that the median survival benefit for the study was shown to be about 11 to 12 days, Moore emphasized that picking a single point on a survival curve was not the proper measure for evaluating the curve as a whole. (D.I. 227 at 915:24-916:11)

underlying technical questions, such as the nature of the claimed invention, nature and scope of the prior art, the differences between the claimed invention and the prior art, or the motivation of one of ordinary skill in the art to combine [them]." *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1364 (Fed. Cir. 2008). Moore's testimony, therefore, may not be relied upon for obviousness purposes.

53. OSI also adduced evidence that erlotinib has achieved commercial success. According to OSI's expert on economics involving the pharmaceutical industry, Dr. Robert Maness ("Maness"), Tarceva® has worldwide sales of about a billion dollars since its launch and its United States sales have continued to grow. It was the most successful American oncology drug launch with respect to the number of new patients and the fourth largest in terms of revenues. (D.I. 228 at 956:13-958:2, 962:8-964:5) Maness attibutes the success of Tarceva® to erlotinib, which generates the properties that are in demand. (*Id.* at 950:17-23, 951:21-952:5, 978:2-16) While the parties generally agree that Tarceva® is profitable,[24] as Mylan points out, OSI does not point to testimony providing context for these numbers. (D.I. 233 at 45) *See, e.g., In re Cyclobenzaprine*, 2012 WL 1320225 at *14, n.6 ("[C]ourts must exercise care in assessing proffered evidence of objective considerations, giving such evidence weight only where the objective indicia are attributable to the inventive characteristics of the discovery **as claimed** in the patent.") (internal quotations and citation omitted)

[24]Subject to a disagreement of how the relevant market is defined. OSI asserted that Tarceva® has a near 100% market share when the relevant market is defined as Tarceva® and Iressa® – an EGFR antibody drug with limited FDA approval in the United States. Mylan emphasizes that the market should not be so narrowed, due to the fact that OSI listed other "competitors" to Tarceva® on internal documents. The court need not define the relevant market as its opinion does not rest on this fact.

(emphasis added).

4. Conclusion

54. In view of the foregoing, the court finds that the RE '065 patent is valid. While the "motivation to select and modify a lead compound need not be explicit in the art" under the flexible rubric of *KSR*, Mylan has not met its burden to demonstrate that a person of ordinary skill in the art would have been motivated to select example 51 of the Barker '226 application as a lead compound and modify the 3'-position with an ethynyl group to arrive at erlotinib. *Daiichi*, 619 F.3d at 1352 (citing *Eisai*, 533 F.3d at 1357 and *Takeda*, 492 F.3d at 1356-57). In reaching its conclusion, the court is in agreement with the PTO, which issued the RE '065 patent over the Barker '226 application on reexamination. (PTX-15; D.I. 227 at 708:5-13)

C. The '221 Patent

55. The court turns next to Mylan's arguments that the '221 patent is invalid as anticipated or as obvious in view of the prior art. As noted above, claim 53 of the '221 patent is directed to the treatment of NSCLC with "a therapeutically effective amount of pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier." Mylan argues that every element of claim 53 of the '221 patent is disclosed in both the '498 patent and an abstract entitled "Development of a Potent, Specific Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase (CP-358,774) as an Anti-Cancer Therapeutic Agent" by Kenneth K. Iwata et. al. (hereinafter, the "1998 Cold Spring Harbor Abstract") (DTX-79). (D.I. 232 at 48)

1. Anticipation

a. Standards

56. An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *See Key Phar. v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *See id.* Proving a patent invalid by anticipation "requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citations omitted). The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). The elements of the prior art must be arranged or combined in the same manner as in the claim at issue, but the reference need not satisfy an *ipsissimis verbis* test. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted).

57. A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is "necessarily present" and not one that may be established by "probabilities or possibilities." *See id.* at 1268-69. That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (emphasis in original) (citations omitted).

b. The '498 patent does not anticipate

58. As discussed above, the '498 patent was reissued as the RE '065 patent. The '498 patent described and claimed erlotinib, and explained that erlotinib is an EGFR inhibitor. The '498 patent provided that, while the "inhibitory properties of the compounds of [f]ormula I vary with structural change as expected, the activity generally exhibited by these agents is in the range of IC_{50} = 0.0001-30 μm." (JTX-3, col. 15:6-11) Claim 14 of the '498 patent was directed to the use of a pharmaceutical composition comprising a therapeutically effective amount of one of the compounds of claim 1 for treating "brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck oesphageal, gynecological or thyroid cancer." (*Id.* at col. 41, ll. 61-63; *see also id.* at col. 44, ll. 3-8 (claim 23), col. 44, ll. 23-27 (claim 29))

59. Contrary to Mylan's contention, however, claims 14, 23 and 29 of the '498 patent do not disclose using erlotinib for the treatment of "lung cancer," rather, they refer to the thousands of compounds encompassed by formula I in the treatment of various cancers. Even if one were to limit the universe to the 12 broad categories of cancers

recited in claim 14, with 105 exemplified compounds, there would still be at least 1,260 combinations of possible treatments.[25] There is no disclosure or direction in the '498 patent that one should select erlotinib and NSCLC out of all of the possible combinations. As OSI's expert Dr. Alan Sandler ("Sandler")[26] testified, an oncologist would not read the '498 patent to teach that every compound disclosed would be a treatment for every disease disclosed.[27] (D.I 227 at 845:11-847:19) The court found Sandler's testimony convincing, and concludes that the '498 patent does not disclose all of the elements of claim 53 as arranged or combined in the same manner as in the claim – i.e., erlotinib for the treatment of NSCLC. *In re Gleave*, 560 F.3d at 1334.

c. The 1998 Cold Spring Harbor Abstract

60. The 1998 Cold Spring Harbor Abstract is part of a collection of abstracts "presented at the Special Anniversary Cold Spring Harbor Winter Conference on Pathways to Cancer" between March 11-14, 1998. (DTX-79) It is Mylan's position that, after their erlotinib patent application was filed, the Pfizer and OSI scientists publicly described the use of erlotinib for treating NSCLC in the 1998 Cold Spring Harbor Abstract. Mylan's expert, Dr. Mark Ratain ("Ratain"), a renowned oncologist from the University of Chicago Medical Center, testified that the 1998 Cold Spring Harbor Abstract expressly discloses every element of claim 53 of the '221 patent except for the

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[25]Mylan points out that OSI advances no evidence in support of its calculations, however, it does not argue that OSI's calculations are incorrect. (D.I. 234 at 21, n.17)

[26]Professor of Medicine and the Chief of the Division of Hematology Oncology at The Oregon Health and Science University.

[27]The parties agree that a person of ordinary skill in the art for the '221 patent is a medical oncologist, unlike the '498 patent, which was directed to a medicinal chemist.

carrier. (D.I. 224 at 63:18-24) The abstract discloses the erlotinib compound when referring to "CP-358774." (*Id.* at 87:19-88:2) Ratain testified that erlotinib's use in treating NSCLC is disclosed in the following statement:

> The elevated expression of EGFR has frequently been associated with breast cancer, gliomas, pancreatic cancers, non-small cell lung cancers and squamous cell tumors of the head and neck. CP-358,774 is a selective and potent inhibitor of isolated human EGFR with an IC_{50} of 2 nM[.]

(DTX-79 at OSI00941044) Further, the abstract reaffirms using erlotinib: "CP-358,774, as a potent, specific inhibitor of the tyrosine kinase activity of EGFR has the potential of providing a highly targeted cancer therapeutic for a wide range of cancers which would be well tolerated." (*Id.*; D.I. 224 at126:19-23) Erlotinib's dosage for oral administration is disclosed as "ED50=10mg/kg qd x 5." (DTX 79; D.I. 224 at 100:6-17) While the abstract does not expressly disclose a carrier, it is Mylan's position that the use of a carrier is inherent in orally administered drugs. (D.I. 224 at 128:11-18; *see also id.* at 63:25-64:3 (Ratain has never prescribed a drug not including a carrier), 100:15-17 ("oral administration of a drug implies a carrier"), 127:2-4 (Ratain testifying that a carrier is "inherent")) Absent factual foundation,[28] however, the court finds this generalized testimony falls short of clear and convincing proof that a carrier is "necessarily present." *See Continental Can*, 948 F.2d at 1268-69.

61. Sandler testified for OSI that the 1998 Cold Spring Harbor Abstract describes preclinical *in vitro* and xenograft model studies on DiFi carcinoma cells (colon cancer) and HN5 (head and neck) tumor cells which do not show treatment of NSCLC

[28]For example, data indicating that a carrier is required for the administration of an oral drug of this nature, or other evidence indicating that the authors always or necessarily utilized carriers in their formulations.

with erlotinib. (D.I. 227 at 847:20-849:8) Sandler testified regarding the difference between treatment of an actual tumor and a xenograft model, which is a human tumor that is changed and modified and transferred to animals lacking immune systems for study. The actual tumor has more genetic variability, often with genetic mutations, than cell lines using a xenograft model, which are more uniform and lack interactions with other bodily systems. (D.I. 227 at 847:20-850:15) According to Sandler, "the correlation between activity seen in xenograft models and that ultimately in humans is quite poor." (*Id.* at 850:16-24)

62. Ratain agreed that the xenograft tests disclosed in this abstract were done on tumor models, not human patients. (D.I. 224 at 142:19-146:11) There was no "treatment" of NSCLC in a mammal as recited by claim 53. (*Id.* at 146:4-7 ("[T]hose are not treatment. Those are experiments")) For the foregoing reasons, the court concludes that Mylan has not met its burden to prove anticipation.

2. Obviousness

a. Mylan's evidence

63. Mylan asserts that, "by the time of the purported claimed invention [November 2000], the idea of treating NSCLC with erlotinib was publicly known through multiple sources, including plaintiffs' own disclosures, and a person of ordinary skill in the art had a reasonable expectation of success in using erlotinib to treat NSCLC." (D.I. 232 at 54) Mylan does not present its obviousness case in terms of specific proffered combinations, rather, it makes its argument in broad terms and lists collections of references it argues support each point. In summary:

- While the '498 patent does not include the term "NSCLC," "many other

prior art references made it clear that EGFR inhibitors—and erlotinib in particular—were being made as therapeutic compounds for treating NSCLC. (*See, e.g.*, DTX-2; DTX-3; DTX-8; DTX-34; DTX-63; DTX-102; DTX-389; DTX-414; DTX-427)"

- "Numerous prior art references also showed the anti-tumor efficacy, tolerability and dosing of EGFR inhibitors, including erlotinib, for treating NSCLC." In addition to the '498 patent and 1998 Cold Spring Harbor Abstract, "[n]umerous publications also disclosed the correlation between EGFR inhibitors and treatment of NSCLC." (DTX-414 at pp. 364-366, 372; DTX-3 at abstract, p. 267; DTX-2 at p. 91; DTX-102 at TEVAERLOT0127069 [ ])"

- "[P]laintiffs' own documents disclose the development of erlotinib for treating NSCLC." (DTX-8, Abstract Nos. 4248 & 4249; DTX-34; DTX-427 at 3; DTX-63; DTX-389)

- "The evidence established that: erlotinib is orally bioavailable; it inhibits EGFR in a potent and selective manner; it is effective against EGFR-overexpressing tumors implanted in mice; and its dose ranges for humans will likely be between 50 and 500 mg." (DTX-8 at OSI03158618; DTX-34 at OSI00645487; DTX-66 at OSI01882132; DTX-79 at OSI00941044; DTX-205A at p. 388a; DTX-389 at 563)

- "[B]ecause of the known association of EGFR with NSCLC and the lack of any similar association with SCLC, a person of ordinary skill in the art would immediately think of NSCLC in the context of an EGFR inhibitor such as erlotinib." (DTX-433 at 310; DTX-443 at 135; DTX-414 at 365)

(D.I. 232 at 54-57)

64. Mylan does not specifically address each possible combination of the aforementioned evidence. Certain of the references are addressed in Mylan's cited testimony in support of its position, as follows. (*Id.*) Ratain testified that DTX-414, a chapter from the book entitled "Lung Cancer" (1993), provided that "EGF receptors. . . were found on non-small cell lung cancer lines, and were absent on small cell lines." The conclusions of this work "really was that EGFR was found on squamous carcinoma of the lung, was found in adenocarcinoma of the lung, and was not found on small cell

carcinoma of the lung." (D.I. 224 at 74:20-77:8) The second (1998) edition of this book (DTX-433) provided that EGFR pathways are overexpressed in NSCLC tumors and not in SCLC tumors. (*Id.* at 106:3-108:15)[29]

65. Mylan also cites to Ratain's testimony regarding DTX-3, a 1996 publication from the British Journal of Cancer entitled "Expression of Epidermal Growth Factor Receptor in Human Lung Tumors." This article noted that "monoclonal antibodies against the EGFR may be helpful diagnostically in differentiating small cell from non-small cell lung cancer and may also be important in elucidating biological differences in primary lung cancer . . . because they saw EGFR only in non-small cell lung cancer." (D.I. 224 at 78:23-79:25) Another article, published in the British Medical Bulletin in 1991 (DTX-2), also stated that the EGF receptor is not overexpressed in SCLC. (*Id.* at 80:1-81:23) Finally, European patent No. 0 566 226 A1 (DTX-102) taught the use of EGFR tyrosine kinase inhibitors for the treatment of squamous cell carcinoma of the lung, a type of SCLC. (*Id.* at 81:24-83:14) Karen Ferrante ("Ferrante"), an inventor of the '221 patent, testified (by deposition) that if she "saw expression of EGFR and lung cancer together, [her] mind [would] leap to non-small cell lung cancer." (D.I. 227 at 926:12-18)

66. Also with respect to the disclosures of the prior art, Mylan cites testimony by Ratain regarding two abstracts by Pfizer and OSI. The first discloses that erlotinib is effective in the HN5 tumor line ("an overexpressing model") at the equivalent to a dose of 50 milligrams a day in a human. (D.I. 224 at 88:3-15; DTX-8, Abstract No. 4249)

[29]OSI objected to the foregoing testimony as being outside the scope of Ratain's expert report.

The second abstract suggests that a dose as high as 500 milligrams per day could be given, and provides that erlotinib "has potential for the treatment of tumors that are dependent on the EGFR pathway for proliferation." (D.I. 224 at 88:18-89:11; DTX-8, Abstract No. 4248) Additionally, a 1997 Parke-Davis article (titled "Inhibitors of Tyrosine Kinase") "discusses progress with erlotinib, stating that it was disclosed at the 1997 conference of the AACR [a]nd then provid[es] dosing information." (D.I. 224 at 98:15-18; DTX-389) In OSI's 1998 10-K filing,[30] OSI stated that CP358774 (erlotinib) targets a variety of cancers, including NSCLC. (D.I. 224 at 110:20-24; DTX-427)

b. OSI's evidence

67. Both Ratain and OSI's expert, Sandler, agreed that there were no prior art tests conducted with erlotinib on NSCLC cell lines. (D.I. 227 at 849:13-850:24, 853:21-23; D.I. 224 at 142:19-146:7) The 1998 Cold Spring Harbor Abstract describes preclinical *in vitro* and xenograft model studies on DiFi carcenoma cells (colon cancer) and HN5 (head and neck) tumor cells. (DTX-79; DI. 227 at 847:20-849:8) As discussed above, Sandler testified that xenograft models differ from actual tumors, and there is "poor" correlation between the two. (D.I. 227 at 847:20-850:24)

68. OSI also points to Sandler's testimony that several other of Mylan's cited references disclose preclinical *in vitro* tests and tests in xenograft models. (D.I. 227 at 854:2-24 (regarding DTX-8) (head and neck cancer xenograft models, one NSCLC xenograft but not with erlotinib); *id.* at 853:2-853:23 (regarding DTX-34) (head and neck

[30]OSI objected to Mylan's use of a 10-K filing as prior art; the court noted the objection. In view of its holding, the court need not resolve the evidentiary issues raised by OSI.

xenograft models); *id.* at 855:30-25 (regarding DTX-389) (head and neck cancer *in vitro* tests with erlotinib))

69. The '498 patent provides an exemplary (and broad) range of *in vitro* data (IC_{50} = 0.001-30μM) and generally references treatment of a "variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors)." (JTX-3 at col. 14, ll. 1-30, col. 15, ll. 3-10) Sandler testified that, while "lung" cancer was listed as an application, a person of ordinary skill in the art would not expect to achieve success in lung cancer[31] with erlotinib specifically, one of 100 different compounds disclosed. (D.I. 227 at 845:17-847:12 (the '498 patent is "extremely broad"))

70. With respect to the disclosures that EGFR pathways are overexpressed in NSCLC tumors, OSI argues that the "mere fact that NSCLC overexpresses EGFR did not suggest to a person of skill that erlotinib would be useful to treat NSCLC." (D.I. 233 at 56) Ratain conceded that the notion that a tumor which overexpressed EGFR would respond to EGFR inhibitors was a hypothesis that was in question in 1999. (D.I. 224 at 138:2-9 ("one skilled in the art did not understand the clinical significance of overexpression of EGFR in cancer"), 139:9-140:3 (overexpression as a predictive biomarker "has not been proven"), 152:23-153:11 ("the prognostic significance of overexpression in lung cancer tissue was unresolved" and "poorly understood in normal

[31]Even assuming that lung cancer is synonymous with NSCLC. While evidence was presented on both sides of the issue, the court's decision does not require explicit findings in this regard.

and diseased states")) Excerpts from several of Mylan's proffered prior art references confirm this testimony, for example:

- "Taken as a whole, the[ ] studies suggest that the overexpression of EFGR and its ligand TGF-α is a frequent event, occurring in at least half of all NSCLC but does not clearly correlate with clinical or pathological indicators of aggressive tumor behavior." (DTX-443 at 135)

- "Ultimately, clinical studies are required to determine the prevalence of human tumors that are dependent on EGFR for proliferation, as well as the clinical toleration of an inhibitor of the EGFR kinase in patients." (DTX 34 at 4846)

- "The prognostic significance of overexpression in lung cancer tissue is unresolved. Overexpression of EGF receptor has been reported to correlate with poor prognosis [ ] or to have no prognostic significance [ ]." (DTX-365 at 369)

Sandler testified as to these references and concluded that there is no proof that overexpression of EGFR is the cause of NSCLC and, commensurately, a person of ordinary skill in the art would not have had a reasonable expectation that inhibiting EGFR would result in the treatment of NSCLC. (D.I. 227 at 837:2-840:11)

71. OSI also points to evidence of secondary considerations of nonobviousness. With respect to the failure of others, between 1990-2005, only seven of 1,631 drugs studied in Phase II for NSCLC obtained FDA approval. (PTX-124) Almost 90% of Phase III trials in oncology failed and only about 5% of new oncology compounds went from human trial to FDA approval. (*Id.*; D.I. 227 at 810:20-813:14) Although a vast number of small molecule EGFR inhibitors have been patented, only erlotinib has been fully approved by the FDA. (D.I. 227 at 828:8-11; PTX-56) Similarly, Ratain agreed that there was a need in the art for an effective second-line therapy (to chemotherapy) for NSCLC; Tarceva® is such a treatment. (PTX-119; D.I. 228 at 1034:17-1036:11)

c. Discussion

72. Mylan's two primary references against the '221 patent are the '498 patent and the 1998 Cold Spring Harbor Abstract. As discussed above, the '498 patent lists "lung" cancer among possible cancers for which 100 disclosed compounds (including erlotinib) are useful. Mylan does not advance a persuasive rationale for why a person of ordinary skill in the art would have been motivated to select erlotinib for the treatment of NSCLC, a specific subset of "lung" cancer generally.[32] Notwithstanding, the court viewed Sandler's testimony on the lack of any reasonable expectation of success to be persuasive. (D.I. 227 at 845:17-847:12) *See Eisai*, 533 F.3d at 1359 ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [ ] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable") (citation omitted).

73. With respect to the 1998 Cold Spring Harbor Abstract, the court found credible Sandler's testimony that there is poor correlation between xenograft models and the treatment of actual human tumors. (D.I. 227 at 847:20-850:24) Notwithstanding, the cells used in this study were not NSCLC cancer cells.

74. The court also agrees with OSI that disclosures in the art connecting the overexpression of EGFR and NSCLC did not suggest to a person of ordinary skill in the art to use erlotinib, given the absence of proof that EGFR causes NSCLC. (D.I. 227 at 837:2-840:11) *See Eli Lilly & Co. v. Teva Pharms. USA, Inc*., Civ. No. 02-0512, 2004

[32]It is not incumbent on the court to formulate Mylan's best arguments utilizing each of Mylan's cited references in the obviousness section of its brief, absent citation to particular testimony illuminating the disclosures of (and value of) those references.

WL 1724632, *35 (S.D. Ind. July 29, 2004) (No reasonable expectation of success where only "scant information was known about the etiology of [the disease]. Any new method of treatment that proved to be effective would have been unexpected[.]")

75. Finally, the court finds persuasive OSI's evidence on secondary considerations of nonobviousness. Despite a need in the art for an effective drug for treating NSCLC, there exists an almost insurmountable failure rate for new drug candidates. *See gen., Monarch Knitting Mach. Corp. v. Sluzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1988) ("[g]eneral skepticism of those in the art – not amounting to teaching away – is also relevant and persuasive evidence of nonobviousness") (citation and internal quotations omitted). Viewing the record as a whole, the court finds that Mylan did not meet its burden to demonstrate that the '221 patent is invalid as obvious by clear and convincing evidence.

III. CONCLUSION

76. In view of the foregoing, the court concludes that Mylan has not proven, by clear and convincing evidence, that claims 1, 2, 4, 8, 34, and 35 of the RE '065 patent are invalid as obvious in view of the prior art or that claim 53 of the '221 patent is invalid as anticipated or as obvious in view of the prior art.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

OSI PHARMACEUTICALS, INC., PFIZER, INC., and GENENTECH INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 09-185-SLR
MYLAN PHARMACEUTICALS INC.,	)	
Defendant.	)	

JUDGMENT IN A CIVIL CASE

For the reasons stated in the opinion issued this same date;

IT IS ORDERED AND ADJUDGED that judgment be and is hereby entered in favor of plaintiffs OSI Pharmaceuticals, Inc., Pfizer, Inc. and Genentech Inc. and against defendant Mylan Pharmaceuticals Inc.

Dated: May 1, 2012

United States District Judge

Francesca Scarpato
(By) Deputy Clerk