Filed on behalf of OSI Pharmaceuticals, LLC and Genentech, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OSI PHARMACEUTICALS, LLC,
and GENENTECH, INC.,

Petitioners,

v.

Patent Owner of

U.S. Patent No. 7,838,512 to Kufe et al.

IPR Trial No. IPR2016-01034

PETITION FOR INTER PARTES REVIEW OF CLAIMS 1-3 & 5-6 OF U.S. PATENT NO. 7,838,512 UNDER 35 U.S.C. §312 AND 37 C.F.R. §42.104

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STATUTES, RULES, AND REGULATIONS

I. Introduction

Petitioners OSI Pharmaceuticals, LLC, and Genentech, Inc., request *inter partes* review of claims 1-3 and 5-6 (the "Challenged Claims") of U.S. Patent No. 7,838,512 B1 (Ex. 1001) (the "'512 patent"), which is assigned to Arch Development Corp. and Dana-Farber Cancer Institute, Inc. (collectively, "Patent Owners").

The '512 patent broadly claims methods of administering ***any*** chemotherapeutic DNA damaging agent in combination with ***any*** low molecular weight tyrosine kinase inhibitor, and includes statements of purpose and function that result from administering this combination. But this basic concept was not new. The prior art taught administering the same claimed combination of agents and provided more disclosure supporting the efficacy of the combination than does the '512 patent.[1] Even the mechanism of action that the '512 patent discusses had been proposed previously. Accordingly, the claims would have been obvious.

This Petition shows that the Challenged Claims are unpatentable based on four grounds:

[1] As Petitioners contend in a related litigation, the disclosure of the '512 patent is insufficient to satisfy the requirements of 35 U.S.C. §112. The prior art cited in this Petition provides equal or greater disclosure than the '512 patent.

First, the Challenged Claims are obvious over Honma, *Induction of Erythroid Differentiation of K562 Human Leukemic Cells by Herbimycin A, an Inhibitor of Tyrosine Kinase Activity*, 49 Cancer Res. 331 (1989) (Ex. 1003) ("Honma"), a printed publication qualifying as prior art under §102(b) published more than five years before the earliest possible priority date of the '512 patent, in view of the knowledge of a person of ordinary skill in the art ("POSA"). Honma teaches exactly what the '512 patent later claimed—i.e., using a low molecular weight tyrosine kinase inhibitor (herbimycin A, one of the preferred inhibitors disclosed in the '512 patent) in combination with a chemotherapeutic DNA damaging agent (Adriamycin) to treat cancer. Honma demonstrates that the combination enhances antiproliferative effects in human leukemia cells and suggests use of the combination for treating leukemia.

Second, as discussed in detail below, Honma in view of the knowledge of a POSA and two references involving the same tyrosine kinase inhibitor (i.e., herbimycin A) or inhibition of the same tyrosine kinase protein, renders all of the Challenged Claims obvious.

Third, in view of the knowledge of a POSA, the Challenged Claims are obvious over Akinaga, *Enhancement of Antitumor Activity of Mitomycin C In Vitro and In Vivo by UCN-01, a Selective Inhibitor of Protein Kinase C*, 32 Cancer Chemotherapy & Pharmacology 183 (1993) (Ex. 1004) ("Akinaga"), a printed

publication that is §102(b) art (or at a minimum §102(a) art), published nine months before the earliest claimed priority date of the '512 patent and over fifteen months before the earliest priority date to which the claims are actually entitled. Akinaga teaches that the combination of the chemotherapeutic DNA damaging agent (mitomycin C ("MMC"), which is also disclosed in a preferred embodiment in the '512 patent) and a low molecular weight tyrosine kinase inhibitor (UCN-01) produces cell killing effects *in vitro* and *in vivo*. Akinaga discloses *in vivo* tests in mice and proposes clinical trials using this combination to treat human cancer patients.

Fourth, as discussed in detail below, Akinaga in view of the knowledge of a POSA and three references involving the same tyrosine kinase inhibitor (UCN-01) or its close structural analog renders all of the Challenged Claims obvious.

This Petition—supported by the Declaration of Dr. Alan Eastman, Ph.D. (Ex. 1002), a leading cancer biologist who has published extensively on the molecular mechanisms underlying cancer—presents analysis and evidence that was not before the Examiner during prosecution. It shows that the Patent Office allowed the '512 patent's claims because it did not have a complete picture of the relevant prior art. For example, Honma was not before the Examiner. The prosecution record did not reflect Honma's disclosure that herbimycin A, the preferred low molecular weight tyrosine kinase inhibitor of the '512 patent,

enhanced the antitumor effect of chemotherapeutic DNA damaging agents, nor did it reflect that Honma recommended the use of such combination therapy in patients more than five years before the earliest claimed priority date. And, although Akinaga was considered by the Examiner and the Board during prosecution of one of the '512 patent's earlier family members, explicit disclosure in Akinaga establishing that UCN-01 ***is*** a tyrosine kinase inhibitor was neither identified nor appreciated.

Petitioners therefore request that this *inter partes* review be instituted and that claims 1-3 and 5-6 be found unpatentable and canceled.

II. Mandatory Notices

A. Real Parties in Interest

OSI Pharmaceuticals, LLC, and Genentech, Inc., submit this Petition. Astellas US LLC, Astellas US Holding, Inc., Astellas Pharma Inc., and Roche Holdings, Inc. are real-parties-in-interest.

B. Related Matters

The Challenged Claims have been asserted against Petitioners in *Arch Development Corp. et al. v. Genentech, Inc. et al.*, No. 1:15-cv-6597 (N.D. Ill.).

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III. Certification of Grounds for Standing

Petitioners certify pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioners are not

barred or estopped from requesting an *inter partes* review on the grounds identified in this Petition.

IV. Overview of Challenge and Relief Requested

A. Grounds of Challenge

Under Rules 42.22(a)(1) and 42.104(b)(1)-(2), Petitioners request cancellation of claims 1-3 and 5-6 of the '512 patent as unpatentable under 35 U.S.C. §103 based on the following grounds.

Ground	35 U.S.C. §	Claims	References
I	103	1-3, 5-6	Honma, in view of knowledge of a POSA
II	103	1-3, 5-6	Honma, in view of knowledge of a POSA, Honma 1992, and McGahon
III	103	1-3, 5-6	Akinaga, in view of knowledge of a POSA
IV	103	1-3, 5-6	Akinaga, in view of knowledge of a POSA, Seynaeve, Friedman, and Tam

B. Relief Requested

Petitioners request that the Board cancel the Challenged Claims because they are unpatentable under 35 U.S.C. §103.

V. Overview of the State of the Art and the '512 Patent

A. The State of the Art

By 1994, the effects of chemotherapeutic DNA damaging agents and tyrosine kinase inhibitors, as well as their use in combination, were known to a POSA.

1. Tyrosine kinases were known to play a role in certain cancers.

Tyrosine kinases are enzymes that catalyze the phosphorylation of a substrate by attaching a phosphoryl group to a tyrosine amino acid residue on the substrate. Tyrosine kinases were known to be involved in cell signaling pathways that control cell growth, differentiation (i.e., development of a precursor cell into a particular cell type via a series of intracellular events), and cell death. (Eastman Decl. ¶31-38 (Ex. 1002).) Elevated tyrosine kinase activity has been associated with cancer because it can promote abnormal cell proliferation. (*Id.* ¶37.) Before 1994, cancer researchers had begun investigating tyrosine kinase inhibitors as potential anti-cancer agents. (*Id.* ¶45.) Researchers also began testing these inhibitors in combination with traditional chemotherapeutic agents, which work by damaging a cell's DNA. (*Id.* ¶¶39-44, 48-56.)

The '512 patent says that tyrosine kinase activities were "known to be associated with the oncogene products of the retroviral src gene family, and also

with several cellular growth factor receptors such as that for epidermal growth factor" ("EGFR"). ('512 patent at 19:13-16 (Ex. 1001).)

2. The effects of DNA damaging agents on intracellular events were known.

The '512 patent explains that DNA damaging agents were known to affect cancer cells by causing "activation of DNA repair, cell cycle arrest, and lethality." (*Id.* at 1:32-35.) By 1994, it was well known that the cell cycle involves progression through four phases: G_1 (growth phase); S (copying of DNA); G_2 (rapid growth in preparation for mitosis/cell division); M (mitosis/cell division). (Eastman Decl. ¶¶40-41 (Ex. 1002).) The cell cycle can arrest in G_1, S and G_2 to allow cells with damaged DNA to repair their DNA. (*Id.* ¶42.) In part, these "checkpoints" are regulated by tyrosine kinases. (*Id.* ¶44.) Cells with damaged DNA that advance to the M phase, however, cannot properly divide and instead die. (*Id.*)

3. Tyrosine kinase inhibitors were known in the art.

Some of the first tyrosine kinase inhibitors identified were small molecules (i.e., low molecular weight compounds) like herbimycin A (discovered in 1979), UCN-01 (discovered in 1987), tyrphostins (first synthesized in the late 1980s), and natural products like erbstatin (discovered in 1991). (*Id.* ¶46 (citing Omura et al., *Herbimycin, a New Antibiotic Produced by a Strain of* Streptomyces, 32 J.

Antibiotics 255 (1979) (Ex. 1005); Takahashi et al., *UCN-01, a Selective Inhibitor of Protein Kinase C from* Streptomyces, 40 J. Antibiotics 1782 (1987) (Ex. 1006); Gazit et al., *Tyrphostins I: Synthesis and Biological Activity of Protein Tyrosine Kinase Inhibitors*, 32 J. Medicinal Chemistry 2344 (1989) (Ex. 1007); Umezawa et al., *Studies on a New Epidermal Growth Factor-Receptor Kinase Inhibitor, Erbstatin, Produced by MH435-HF3*, 39 J. Antibiotics 170 (1986) (Ex. 1008)).) The '512 patent lists low molecular weight tyrosine kinase inhibitors that were known as of 1994, citing numerous prior art publications. ('512 patent at 19:10-20:39 (Ex. 1001).) Indeed, the compounds listed in the'512 patent consist solely of already-discovered compounds—the '512 patent neither disclosed nor claimed a new tyrosine kinase inhibitor. (Eastman Decl. ¶¶46, 60 (Ex. 1002).)

4. Combination therapies of tyrosine kinase inhibitors and DNA damaging agents were known to be effective.

Before 1994, multiple groups in addition to the Honma and Akinaga authors had considered combinations of tyrosine kinase inhibitors with chemotherapeutic DNA damaging agents. (*Id.* ¶¶48-56.) For instance, Fan discloses using cisplatin (another chemotherapeutic DNA damaging agent) in combination with a tyrosine kinase inhibitor—specifically, an anti-EGFR antibody—in a mouse model. (Fan et al., *Antitumor Effect of Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies Plus Cis-Diamminedichloroplatinum on Well Established A431 Cell*

Xenografts, 52 Cancer Res. 4637, 4638 (1993) (Ex. 1009) ("Fan"); Eastman Decl. ¶51 (Ex. 1002).) Fan suggests that the combination "may have application in the therapy of human malignancies" and notes the "excellent rationale for" and "interest in combining cytotoxic chemotherapeutic agents with growth-inhibitory biological agents." (Fan at 4637 (Ex. 1009); Eastman Decl. ¶51 (Ex. 1002).) And Monti, published in 1992, discloses that the combination of genistein (one of two small-molecule tyrosine kinase inhibitors actually tested in the '512 patent), and doxorubicin, a chemotherapeutic DNA damaging agent, had synergistic antiproliferative effects in human breast cancer cells. (Monti et al., *Antiproliferative Effects of Genistein and Doxorubicin Against ER-Positive and -Negative Human Breast Cancer Cell Lines*, 33 Proc. Am. Assoc. Cancer Res. 442 (1992) (Ex. 1010); Eastman Decl. ¶52 (Ex. 1002).)

Tyrphostins were known to have "antiproliferative effects on human squamous cell carcinoma *in vitro* and *in vivo*," ('512 patent at 20:4-6 (Ex. 1001)), and, as Yoneda reports, "prolonged the life span of [the] tumor-bearing animals," (Yoneda et al., *The Antiproliferative Effects of Tyrosine Kinase Inhibitors Tyrphostins on a Human Squamous Cell Carcinoma In Vitro and in Nude Mice*, 51 Cancer Res. 4430, 4430, 4432, 4434 & fig. 8 (1991) (Ex. 1011).) Yoneda also suggests that tyrphostins "will have greater utility when used in conjunction with

drugs such as cisplatinum and [Adriamycin]," both well-known chemotherapeutic DNA damaging agents. (*Id.* at 4434; Eastman Decl. ¶53 (Ex. 1002).)

By 1994, it also was known that cell cycle arrest could be overcome using combinations like those claimed in the '512 patent. (Eastman Decl. ¶54 (Ex. 1002).) For example, Tam demonstrates that a kinase inhibitor called staurosporine—which inhibits the tyrosine kinases v-Src and EGFR, among others—caused cancer cells to "bypass[] the cell cycle checkpoint that prevents the onset of mitosis in the presence of damaged DNA," resulting in reduced survival of target cells. (Tam et al., *Staurosporine Overrides Checkpoints for Mitotic Onset in BHK Cells*, 3 Cell Growth & Differentiation 811, 811 (1992) (Ex. 1012) ("Tam"); *see also* Eastman Decl. ¶54 (Ex. 1002).) Similarly, Lau discloses that caffeine—another compound that can inhibit tyrosine kinases—allowed cells that had been treated with nitrogen mustard, a DNA damaging agent, to "divide without finishing the repair processes," resulting in cell death. (Lau et al., *Mechanism by Which Caffeine Potentiates Lethality of Nitrogen Mustard*, 79 Proc. Nat'l Acad. Sci. 2942, 2942 (1982) (Ex. 1013) ("Lau"); *see also* Eastman Decl. ¶55 (Ex. 1002).) By 1994, it also was understood that UCN-01 prevents cell cycle arrest and allows cells with damaged DNA to undergo mitosis. (Seynaeve et al., *Cell Cycle Arrest and Growth Inhibition by the Protein Kinase Antagonist UCN-01 in Human Breast*

Carcinoma Cells, 53 Cancer Res. 2081, 2085 (1993) (Ex. 1014) ("Seynaeve"); Eastman Decl. ¶55 (Ex. 1002).)

Thus, before the '512 patent's priority date, numerous groups had explored combinations involving tyrosine kinase inhibitors and chemotherapeutic DNA damaging agents.

B. Brief Description of the '512 Patent

The '512 patent claims methods of administering a chemotherapeutic DNA damaging agent in combination with a low molecular weight tyrosine kinase inhibitor. (*See, e.g.*, '512 patent at claim 1 (Ex. 1001).)

The specification lists DNA damaging agents (including Adriamycin and MMC) (*id.* at 18:14-19:7 (Ex. 1001)) and tyrosine kinase inhibitors (for example, genistein, herbimycin A and tyrphostins) (*id.* at 19:28-20:39)—all of which were known in the prior art. (Eastman Decl. ¶¶58-60 (Ex. 1002).) The only experimental data the specification discloses relating to chemotherapeutic DNA damaging agents are experiments designed to examine the activity of Src family kinases in response to the DNA damaging agent MMC. ('512 patent at 9:4-14:5 (Ex. 1001); Eastman Decl. ¶63 (Ex. 1002).) The only low molecular weight tyrosine kinase inhibitors that were tested in combination with DNA damaging agents were herbimycin A and genistein. ('512 patent at 9:4-18:14 (Ex. 1001);

Eastman Decl. ¶63 (Ex. 1002).) All of these studies were *in vitro*, and none of them measured growth inhibition or showed an increase in cell death.

The ’512 patent proposes that combining a DNA damaging agent with a tyrosine kinase inhibitor improves chemotherapeutic intervention by altering the cell’s response to the DNA damaging agent. (’512 patent at 3:36-5 (Ex. 1001); *see also id.* at 18:4-8.) Citing prior art, the specification proposes that cells exposed to DNA damaging agents undergo a lengthening of the cell cycle’s G_2 phase, allowing more time for DNA repair and thereby increasing cell survival. (*Id.* at 3:36-5, 13:33-52 (Ex. 1001) (citing Lau).) The ’512 patent further states that tyrosine kinase inhibitors could force cells to progress more quickly past this G_2 arrest into mitosis, thereby converting reparable damage into lethal damage. (*Id.* at 3:38-42, 19:20-27.)

None of this was new. (Eastman Decl. ¶¶57-67 (Ex. 1002).) Combination therapies involving tyrosine kinase inhibitors and DNA damaging agents already had been proposed, and the rationale for such combinations was well understood. (*Id.* ¶¶48-56, 63-67.) The mechanism of action suggested by the ’512 patent was also discussed in the prior art. (*Id.*)

C. Summary of the ’512 Patent’s Prosecution History

The ’512 patent issued November 23, 2010, from U.S. Application No. 11/381,311 (“the ’311 application”), filed May 2, 2006. (’512 patent at cover (Ex.

1001).) The '311 application is the fourth application in a series that claims priority to U.S. Application No. 08/192,107 (the "'107 application"), filed February 4, 1994.

Akinaga, on which Petitioners rely in Grounds III and IV, was addressed during prosecution of the grandparent of the '512 patent— U.S. Patent No. 6,524,832 (Ex. 1015) (the "'832 patent"). In response to a rejection over Akinaga, Patent Owners argued (incorrectly) that the compound UCN-01 inhibits only protein kinase C ("PKC")—not any tyrosine kinases. (11/13/1995 Resp. at 6-7 (Ex. 1016) ("Akinaga et al. appears to show simply that some protein kinase inhibitors (not tyrosine kinase inhibitors) may be used with mitomycin C as an anti-tumor combination.") (emphasis in original).) Patent Owners appealed the Akinaga rejection to the Board, which ultimately concluded that the Examiner failed to "identify[] precisely where his references teach protein tyrosine kinases." (9/19/2001 Decision at 5 (Ex. 1017).) In fact, Akinaga expressly discloses that UCN-01 inhibits "$pp60^{v\text{-}src}$" as part of a table labeled "[i]nhibition of protein kinase," and clearly states that $pp60^{v\text{-}src}$ is "v-src ***tyrosine kinase***" under that table. (Akinaga at 184 tbl.1 (Ex. 1004) (emphasis added).)

During prosecution of the '512 patent, Akinaga was cited in an IDS, but was not relied on by the Examiner. (10/2/2006 IDS at 4 (Ex. 1033).) Honma was not

of record. Other prior art rejections were overcome based on an incomplete picture of the prior art.

For instance, to overcome a rejection over Yoneda (1/4/2010 Office Action at 5 (Ex. 1018)), which discloses small molecule tyrosine kinase inhibitors and suggests their use in combination with DNA damaging agents (*id.* at 6), Patent Owners submitted a §1.132 Declaration by the inventor, Dr. Kufe. In his declaration, Dr. Kufe suggested that the claimed combinations were counter-intuitive, stating that:

> At the time the patent application was filed, it was commonly understood that small molecule TKIs inhibit or suppress cell division while DNA damaging agents are more effective at killing rapidly dividing cancer cells …. Therefore, it was expected that if a combination of these agents was used, cells reactive to TKI would not be rapidly dividing, so not as responsive to DNA damage.

(4/16/2010 Kufe Decl. ¶5 (Ex. 1019); 4/23/2010 Resp. to Office Action at 5-8 (Ex. 1020).) This declaration ignored the fact that multiple chemotherapeutic DNA damaging agent and tyrosine kinase inhibitor combinations had already been assessed for their impact on cancer, yielding favorable results, and that the prior art provided similar mechanistic explanations to those discussed in the ’512 patent. (Eastman Decl. ¶64-67 (Ex. 1002).)

The ’512 patent is subject to a Certificate of Correction clarifying that the claims are directed to the use of “chemotherapeutic” DNA damaging agents.

D. Priority Date

Despite its priority claim, none of the ’512 patent’s claims is entitled to a February 4, 1994 priority date based on the ’107 application. All of the ’512 patent’s claims, as corrected, require a “***chemotherapeutic*** DNA damaging agent.” (’512 patent at claims (Ex. 1001) (emphasis added).) Yet the ’107 application focused exclusively on ***radiation*** as a DNA damaging agent. Chemotherapeutic DNA damaging agents are chemical compounds usually administered via injection or pill, and radiation is a considerably different modality. (Eastman Decl. ¶¶68-69 (Ex. 1002).) Patent Owners first referred to potential combination therapies involving chemotherapeutic DNA damaging agents in new matter added in a continuation-in-part application filed September 19, 1994.[2] (Redline Comparing the 2/4/1995 Application to the 9/19/1994 Application (Ex. 1021); Eastman Decl. ¶68-70.) Because the ’107 application lacks written description support for the limitation “chemotherapeutic DNA damaging agent,” the earliest priority date to

[2] The ’512 patent reports the CIP’s filing date as Aug. 19, 1994, but the patent that issued from that application indicates the filing date was Sept. 19, 1994. (’832 patent at certificate of correction (Ex. 1015).)

which the '512 patent's claim may be entitled is September 19, 1994. *See* 35 U.S.C. §120. Regardless of which priority date applies, the Challenged Claims are obvious.

VI. Person of Ordinary Skill in the Art

A POSA in 1994 would have held an M.D. or Ph.D. in molecular biology, biochemistry, pharmacology, or a related field and have had several years of experience working in cancer research. (Eastman Decl. ¶19 (Ex. 1002).)

VII. Claim Construction

The '512 patent expired on April 8, 2015. "[T]he board's review of the claims of an expired patent is similar to that of a district court's review." *In re Rambus, Inc.*, 694 F.3d 42, 46 (Fed. Cir. 2012); *cf.* Amendments to PTAB Rules, 81 Fed. Reg. 18753, 18753-54 (Apr. 1, 2016). Solely for purposes of this proceeding, Petitioners propose constructions of certain terms and identify support under the *Phillips* standard. *See Phillips v. AWH Corp.,* 415 F.3d 1303 (Fed. Cir. 2005) (en banc).

A. Preamble

The Challenged Claims' preambles—"[a] method of improving chemotherapeutic intervention in a patient" and "[a] method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention in a

patient"—are not limitations because they only state a purpose and add nothing to the claims.

To be limiting, a preamble must add something to the claim. "A preamble limits [an] invention," for example, "if it recites essential structure or steps." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). "Conversely, a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Id.* (quotation marks omitted).

The Challenged Claims' preambles do not add any structure to the claims or result in any difference in method steps. (Eastman Decl. ¶¶73-74 (Ex. 1002).) The Federal Circuit and district courts have found such preambles non-limiting. *See, e.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374-76 (Fed. Cir. 2001) (finding "a method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity," to be non-limiting); *Teva Pharms. USA, Inc. v. Forest Labs., Inc.*, C.A. No. 13-2002-GMS, 2015 WL 4143277, at *2 & n.3 (D. Del. July 9, 2015) (construing "preamble phrase 'for the administration ... to a human or animal subject for the treatment of pain' ... not to be limiting").

B. "patient"

The term "patient" should be construed to encompass both animal and human subjects. (Eastman Decl. ¶¶76-77 (Ex. 1002).) The specification states that "[t]he present invention also provides advantageous methods for treating cancer that, generally, comprise administering to ***an animal or human patient*** with cancer a therapeutically effective combination of a DNA damaging agent and a tyrosine kinase inhibitor." ('512 patent at 5:50-54 (Ex. 1001) (emphasis added).) Further, "[c]hemical DNA damaging agents and/or inhibitors may be administered to ***the animal***" (*id.* at 5:54-55 (emphasis added)), and "the tumor cells may be contacted with the DNA damaging agent by administering to ***the animal***." (*Id.* at 5:64-67 (emphasis added); *see also id.* at 4:20-21 (referring to "animal or human subject").) Nothing in the specification or file history limits "patient" to human subjects. If Patent Owners "had desired to limit the claims to 'human patients,' [they] could have used that language instead of 'patient.' Since [they] chose to use the broader term[] ... 'patient,' the scope of the claims should reflect [their] choice of words." *Novo Nordisk v. Eli Lilly & Co.*, No. CIV.A. 98-643 MMS, 1999 WL 1094213, at *17 (D. Del. Nov. 18, 1999).

C. "therapeutically effective amount"

Each of the Challenged Claims recites "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor."

"Therapeutically effective amount" should be construed in accordance with its plain and ordinary meaning, i.e., "an amount that would be sufficient to have a desired therapeutic effect." (Eastman Decl. ¶¶79-80 (Ex. 1002); *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1300 (Fed. Cir. 2006) ("A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure."); *Novartis Pharms. Corp. v. Apotex Corp.*, No. 02-cv-8917, 2006 WL 626058, at *4 (S.D.N.Y. 2006) (construing term "a therapeutically effective amount" of calcitonin as meaning "an amount of calcitonin sufficient to produce a desired therapeutic effect").) A POSA reviewing the '512 patent would have understood such effect could be established through *in vitro* or *in vivo* studies. ('512 patent at 4:10-12 (Ex. 1001) ("A number of in vitro parameters may be used to determine the effect produced by the compositions and methods of the present invention."); Eastman Decl. ¶80 (Ex. 1002).)

The '512 patent does not demonstrate any particular therapeutic effect of a low molecular weight tyrosine kinase inhibitor in animals or humans, nor suggest that anything besides the plain and ordinary meaning should apply. The specification refers to a "therapeutically effective amount" of a *combined* amount of the DNA damaging agent and the tyrosine kinase inhibitor, while the claims require that *only* the tyrosine kinase inhibitor be administered in a "therapeutically effective amount." The specification does not provide any particular requirements

regarding the meaning of "therapeutically effective amount" in the context of the actual claim limitations.

D. "apoptosis"

Independent claim 5 recites the term "apoptosis." The specification defines "apoptosis" to mean "***a series of intracellular events that lead to target cell death***." ('512 patent at 5:35-38 (Ex. 1001) (emphasis added).) This definition is consistent with how a POSA would have understood "apoptosis" in 1994 (Eastman Decl. ¶82-83 (Ex. 1002)) and is controlling. *See Phillips,* 415 F.3d at 1316.

E. "improving chemotherapeutic intervention"

Claims 1-3 conclude with "thereby improving chemotherapeutic intervention." It is well established that a clause that merely indicates the intended result of performing the prior step is not limiting. *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."); *Thermal Dynamics Corp. v. TATRAS, Inc.*, No. 04-152-PB, 2004 WL 4957314, at *6 (D.N.H. Dec. 9, 2004) (finding that, for similar reasons as in "whereby" clause cases, "thereby producing a longer wearing electrode" was not a limitation but was merely the result of a prior step in the claim). Because "improving chemotherapeutic intervention" merely identifies the

intended result of performing the prior steps, the clause is not limiting. (Eastman Decl. ¶¶84-85 (Ex. 1002).)

VIII. Ground I: The Challenged Claims Are Obvious over Honma in View of the Knowledge of a Person of Ordinary Skill in the Art.

Honma, published over five years before the '512 patent's earliest effective filing date, discloses administering the combination of herbimycin A (one of only two tyrosine kinase inhibitors actually tested in the '512 patent), with Adriamycin (a chemotherapeutic DNA damaging agent identified as such in the '512 patent) to human leukemia cells. (Eastman Decl. ¶¶88-93 (Ex. 1002).) Honma reports that the combination enhanced antiproliferative effects, and suggests using the combination in treating leukemia. (*Id.* ¶¶92-95.) A POSA would have understood that the combination therapy Honma tests satisfies the functional limitations in the Challenged Claims, that Honma demonstrates that the combination enhances cell death, and that the next step in pursuing Honma's suggestion to use the combination to treat leukemia patients would be to test the combination in animals. Accordingly, Honma, in view of the knowledge of a POSA, renders the Challenged Claims obvious.

A. Claim 1

Claim 1 is obvious over Honma and the knowledge of a POSA at the time of the alleged invention. (Eastman Decl. ¶106-136 (Ex. 1002).)

i. ***"A method of improving chemotherapeutic intervention in a patient, the method comprising"***

As explained above, *see supra* §VII.A, the preamble is not limiting. But even if Patent Owners argue it is limiting, Honma teaches a method of improving chemotherapeutic intervention in a patient. (Eastman Decl. ¶¶107-12 (Ex. 1002).)

Honma discloses that "[n]oncytotoxic concentrations of herbimycin enhanced the antiproliferative effect of Adriamycin ... on K562 cells," which are cells derived from an individual with "human chronic myelogenous leukemia." (Honma at 331 (Ex. 1003); *see also id.* at 333 & fig. 5.) From this disclosure, a POSA would have understood that Honma's combination therapy is an improvement over chemotherapeutic intervention using Adriamycin alone. (Eastman Decl. ¶¶108-09.)

Honma further suggests use of the disclosed combination in patients. (*Id.* ¶109.) For example: "Combination therapy with herbimycin A and its derivatives may be considered for use in the treatment of some types of leukemia where tyrosine kinase activities are implicated as determinants of the oncogenic state." (Honma at 331 (Ex. 1003); *see also id.* at 333 ("Since herbimycin A can have an additive or more than additive effect with some well-known antitumor agents such as Adriamycin ... these combinations may be useful for the treatment of some types of leukemia.").) This discussion of clinical use based on data demonstrating

enhanced antiproliferative effect discloses at least as much as the '512 patent and renders the "in a patient" element of the preamble obvious.

Even if Patent Owners argue claim 1's preamble is not expressly disclosed in Honma, it would have been obvious for a POSA to use the combination disclosed in Honma to improve chemotherapeutic intervention in a patient. A POSA would have been motivated to apply the Honma combination to animals, followed by humans, because that is the normal progression of successful biomedical experiments. (Eastman Decl. ¶110 (Ex. 1002).) For example, Fan did just that, testing a tyrosine kinase inhibitor/DNA damaging agent combination in tumor cell xenografts in mice and proposing that "clinical trials of combination therapy with [the antibody] plus *cis*-DDP chemotherapy will be carried out." (Fan at 4639-41 & figs. 4-6 (Ex. 1009); Eastman Decl. ¶51.)

A POSA thus would have administered the Honma combination to patients with a reasonable expectation of success. Indeed, by 1994, a POSA would have known the doses at which the components of Honma's combination—herbimycin A and Adriamycin—could be administered to patients. In a 1992 publication, Honma disclosed how to dose herbimycin A in tumor-bearing mice. (Honma et al., *Herbimycin A, an Inhibitor of Tyrosine Kinase, Prolongs Survival of Mice Inoculated with Myeloid Leukemia C1 Cells with High Expression of v*-abl *Tyrosine Kinase*, 52 Cancer Res. 4017, 4020, tbl.2 & fig. 4 (1992) (Ex. 1022)

("Honma 1992"); Eastman Decl. ¶¶47, 111-12 (Ex. 1002).) Likewise, a POSA would have understood how to dose Adriamycin in patients, a drug commonly used to treat cancer in humans. (Eastman Decl. ¶¶111-12, 114; *see also* Doxorubicin, *in* Physicians' Desk Reference 832-33 (45th ed. 1991) (Ex. 1023) ("PDR").)

ii. *"administering a chemotherapeutic DNA damaging agent to the patient"*

Claim 1 recites "administering a chemotherapeutic DNA damaging agent to the patient." Honma discloses administering Adriamycin, which the '512 patent concedes is a DNA damaging agent. ('512 patent at 18:54-63 (Ex. 1001).) Further, a POSA would have understood Adriamycin to be a chemotherapeutic DNA damaging agent. (Eastman Decl. ¶114 (Ex. 1002).) As of 1994, Adriamycin had long been used to treat human cancer patients. (*Id.*)

Administration to a patient is discussed above (*see supra* §VIII.A.i) and incorporated by reference here. (Eastman Decl. ¶¶109-15.)

iii. *"administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient"*

Claim 1 recites "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient." Honma discloses administering herbimycin A, which it expressly identifies as a tyrosine kinase inhibitor, to cancer cells. (Honma at 331 (Ex. 1003) ("Herbimycin A, an Inhibitor

of Tyrosine Kinase Activity").) Herbimycin A also is identified as an "[e]xemplary tyrosine kinase inhibitor" in the '512 patent. ('512 patent at 4:39-40, 19:20-21, 19:35-39 (Ex. 1001).) A POSA would have understood herbimycin A to be of low molecular weight. (Eastman Decl. ¶118 (Ex. 1002).) The molecular weight of herbimycin A is 574 daltons. (*Id.* (citing Furusaki et al., *Herbimycin A: An Ansamycin Antibiotic; X-ray Crystal Structure*, 33 J. Antibiotics 781 (1980) (Ex. 1024).)) Small molecules—which Patent Owners distinguished from monoclonal antibodies in prosecution on the basis of their lower molecular weight—are typically understood to have molecular weights less than 900 daltons. (Eastman Decl. ¶118.)

Administration to a patient is discussed above (*see supra* §VIII.A.i) and incorporated by reference here.

Honma also discloses administering herbimycin A in a therapeutically effective amount, i.e., "an amount sufficient to have a desired effect." (*See supra* §VII.C.) First, Honma discloses a "[n]oncytotoxic concentration of herbimycin enhanced the antiproliferative effect of Adriamycin ... on K562 [human leukemia] cells." (Honma at 331 (Ex. 1003).) A POSA would have understood an enhanced antiproliferative effect achieved at noncytotoxic concentration to be a desired therapeutic effect. (Eastman Decl. ¶120 (Ex. 1002).) Second, Honma discloses that the combination of herbimycin A and Adriamycin reduces cell number

compared to a control culture. (Honma at 333 & fig. 5 (Ex. 1003) ("When K562 cells were treated simultaneously with 4×10^{-8} M herbimycin and 1.1×10^{-8} M Adriamycin, the cell number was decreased to less than 20% of that in control culture (Fig. 5).").) A POSA likewise would have understood reducing cancer cell numbers versus a control to be a desired effect for a cancer drug combination. (Eastman Decl. ¶120 (Ex. 1002).) Finally, Honma discloses in Figure 4 that herbimycin A causes differentiation of the leukemia cells. (Honma at 332-33 & fig.4 (Ex. 1003); Eastman Decl. ¶120.) A POSA would have understood the disclosed differentiation as leading to leukemia cell death—as explained in more detail below (*see infra* §VIII.A.v)—a desired effect for a cancer drug combination. (Eastman Decl. ¶120.)

iv. *"wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein"*

Honma discloses that herbimycin A "binds intracellularly to inhibit the activity of more than one tyrosine kinase protein." First, Honma states that "Herbimycin A ... reduced $p60^{src}$ associated protein kinase activity" (Honma at 331 (Ex. 1003)), which a POSA would have understood to be tyrosine kinase protein activity. (Eastman Decl. ¶¶122-23 (Ex. 1002).) Second, Honma shows that herbimycin A inhibits the activity of $p210^{c\text{-}abl}$, another tyrosine kinase protein that primarily phosphorylates itself. (Honma at 333.) The reduction in

phosphorylated $p210^{c\text{-}abl}$ shown by Honma therefore indicates a reduction in $p210^{c\text{-}abl}$ tyrosine kinase activity. (*Id.* at 332-33 fig. 3; Eastman Decl. ¶¶122-23.)

A POSA would have understood that herbimycin A inhibits these tyrosine kinases by intracellular binding (Eastman Decl. ¶121 (Ex. 1002)), as Patent Owners admitted during prosecution. In response to a rejection over an antibody reference, Patent Owners argued that "the small molecule inhibitors of the claimed invention"—which would include the "exemplary" inhibitor herbimycin A, '512 patent at 4:39-40—"work in a completely different manner" from antibodies. (9/11/2009 Resp. at 8 (Ex. 1025).) "***They exert their effects intracellularly by intracellular binding*** and inhibiting one or more tyrosine kinases." (*Id.* (emphasis added).) Indeed, at the time of the alleged invention, a POSA would have understood that low molecular weight compounds bind their targets intracellularly. (Eastman Decl. ¶¶121, 123.)

v. *"wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death"*

It would have been obvious to a POSA reviewing Honma that Adriamycin and herbimycin A act in combination by effecting a series of intracellular events to enhance cell death. Honma teaches (1) that the combination promotes cellular differentiation of a leukemia cell line, which necessarily causes cells to lose their immortality, and thus, to die, and (2) that the combination inhibits $p210^{c\text{-}abl}$, which

enhances cell death by a different mechanism (*see infra* §VIII.C.i, which is incorporated by reference here). In addition, a POSA would have known that herbimycin A alone kills cells, and that the herbimycin A/Adriamycin combination therefore would enhance cell death.

Honma teaches that Adriamycin and herbimycin A act in combination to cause differentiation of K562 human leukemia cells. In K562 cells, induction of differentiation "enhance[s] cell death." Differentiation is the process by which precursor cells undergo a series of changes—including intracellular events—to become a more specialized cell. (Eastman Decl. ¶125-26 (Ex. 1002).) When cells reach the point that they can differentiate no more, they are terminally differentiated, in which state they live out their days and die. (*Id.* ¶¶126-27.)[3]

The K562 human chronic myelogenous leukemia cell line studied in Honma is immortal (i.e., the cells proliferate indefinitely in an undifferentiated state). (*Id.* ¶127.) Inducing K562 cells to differentiate—i.e., to start maturing into hemoglobin producing red blood cells —causes these cells to lose their immortality. (*Id.* ¶¶127-28.)

[3] Although Patent Owners argued during prosecution of a related patent that inducing differentiation is not "cell killing" (11/13/1995 Resp. at 6 (Ex. 1016)),"cell killing" is not a limitation of any of the Challenged Claims.

Figure 4 of Honma discloses that herbimycin A increases the ability of Adriamycin to induce differentiation in K562 cells. (*Id.* ¶129; *see also* Honma at 332 & fig. 4 (Ex. 1003) (showing (1) that herbimycin A alone induced erythroid differentiation of up to 50% of K562 cells after 3 days over a concentration range of 2×10^{-8} M to 6×10^{-8} M; and (2) that, at a constant concentration of Adriamycin (3×10^{-9} M), the same concentrations of herbimycin A induced up to about 50% more differentiation).) Honma describes these results by noting that "herbimycin A and [Adriamycin] have additive or more than additive effects on induction of benzidine-positive cells in suboptimal concentrations," and interprets these data to mean that the combination induces differentiation of the K562 cells. (Honma at 333 (Ex. 1003).)

Thus, Honma discloses that the Adriamycin/herbimycin A combination causes immortal cells to become mortal, thereby enhancing cell death. At a minimum, a POSA would have understood that inducing K562 cells to differentiate into benzidine-positive cells, which are immediate precursors to red blood cells and also mortal, enhances the eventual death of the K562 cells. (Eastman Decl. ¶¶124-29 (Ex. 1002).) Accordingly, a POSA would have understood Honma to teach this limitation.

The claims and specification provide no limits on when cell death must occur. But, even if Patent Owners argue that the claim requires more immediate cell death than results from differentiation, a POSA would have nonetheless understood Honma to disclose this limitation. Adriamycin was well known to cause cell death in many cancer cells. (Eastman Decl. ¶131 (Ex. 1002) (citing Skladanowski et al., *Adriamycin and Daunomycin Induce Programmed Cell Death (Apoptosis) in Tumour Cells*, 46 Biochemical Pharmacology 375 (1993) (Ex. 1034)).) And Herbimycin A alone causes cell death, as the prosecution history for an earlier patent in the '512 patent's priority chain demonstrates. (*Id.* ¶¶131-34.) In a declaration, one of the inventors reported that herbimycin A, on its own, kills cells. (*Id.* ¶¶131-34; 11/21/1995 Weichselbaum Decl. at 2-4 & Ex. 1 (Ex. 1026).) Accordingly, a POSA would have understood that Honma's combination of herbimycin A with the DNA damaging agent Adriamycin enhances cell death. (Eastman Decl. ¶134.)

vi. *"thereby improving chemotherapeutic intervention"*

Claim 1 ends "thereby improving chemotherapeutic intervention." This is a non-limiting statement of intended result. (*See supra* §VII.E.) But, as discussed in Section VIII.A.i, which is incorporated by reference here, even if Patent Owners argue this clause is limiting, Honma discloses it. (Eastman Decl. ¶¶107-12, 135 (Ex. 1002).)

B. Claim 2

Claim 2 is also obvious over Honma in view of the knowledge of a POSA. (*Id.* ¶¶137-47; *see also infra* §X.) Claim 2 shares nearly all of its limitations—specifically, the claim terms discussed in Sections VIII.A.i, VIII.A.ii, VIII.A.iii, VIII.A.vi, which are incorporated by reference here—with claim 1. Claim 2 differs from claim 1 in only two ways. First, it does not require that "the agent and the inhibitor act in combination *by effecting a series of intracellular events* to enhance cell death," but merely that they "act in combination to enhance cell death" (emphasis added). Because Honma renders obvious the narrower form of this limitation in claim 1, as explained in Section VIII.A.v above, it also renders obvious the broader form in claim 2. (Eastman Decl. ¶139 (Ex. 1002).) Second, claim 2 also requires that the tyrosine kinase inhibitor "intracellularly inhibits phosphorylation of downstream effector molecules." Honma teaches this limitation.

i. *"wherein the low molecular weight inhibitor …intracellularly inhibits phosphorylation of downstream effector molecules"*

The '512 patent record shows that herbimycin A intracellularly inhibits phosphorylation of downstream effector molecules. As explained above, Patent Owners admitted during prosecution that herbimycin A "exert[s] [its] effects intracellularly by intracellular binding and inhibiting one or more tyrosine

kinases." (9/11/2009 Resp. at 8 (Ex. 1025); *see also* VIII.A.iv.) The specification also repeats the widely known principle that "[i]nhibition of … activation of … tyrosine kinases prevents or inhibits substrate phosphorylation." ('512 patent at 17:67-18:2 (Ex. 1001); *see also* Eastman Decl. ¶141 (Ex. 1002).) A POSA would have understood that a substrate is a downstream effector molecule of a tyrosine kinase protein. (Eastman Decl. ¶141.)

Furthermore, a POSA would have understood that, once initiated by activation of a tyrosine kinase protein, many of the steps in the signal transduction pathway proceed through phosphorylation of downstream effector molecules (i.e., molecules that are downstream from the tyrosine kinase protein in the pathway). (Eastman Decl. ¶¶35, 140-45.) If the tyrosine kinase is inhibited, signal transduction along the pathway is also inhibited. (*Id.*) Therefore, a POSA would have understood Honma to necessarily disclose the intracellular inhibition of phosphorylation of downstream effector molecules. (*Id.* ¶¶140-46.)

C. Claim 3

Honma, in view of the knowledge of a POSA, also renders claim 3 obvious. (*Id.* ¶148-153; *see also infra* §X.) Claim 3 is very similar to claim 2, and includes claim terms identical to those discussed in Sections VIII.A.i, VIII.A.ii, VIII.A.iii, VIII.B.i, and VIII.A.vi, which are incorporated by reference here. However, instead of requiring that "the low molecular weight inhibitor binds intracellularly

to inhibit the activity of *more than one* tyrosine kinase protein," claim 3 requires that the inhibitor "binds intracellularly to inhibit the activity of *EGFR and at least one other* tyrosine kinase protein." This limitation is obvious over Honma in view of the knowledge of a POSA.

i. *"wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase protein"*

As explained above with respect to claim 1, Honma teaches that "the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein." (*See supra* §VIII.A.iv.) The only difference for this limitation in claim 3 is the requirement that one of those tyrosine kinase proteins is EGFR. This limitation is obvious in light of the knowledge of a POSA.

By 1994, it was known that herbimycin A inhibited the activity of multiple tyrosine kinase proteins, including EGFR. (Eastman Decl. ¶150 (Ex. 1002).) As shown above, Honma discloses that herbimycin A inhibits the tyrosine kinases $p210^{c\text{-}abl}$ and $p60^{src}$. (*See supra* §VIII.A.iv.) As for EGFR, the '512 patent states that "[h]erbimycin A has also been shown to inhibit the autophosphorylation of EGF-stimulated receptors .... Herbimycin A both decreases the receptor quantity and the EGF-stimulated receptor tyrosine kinase activity." ('512 patent at 19:35-39 (Ex. 1001).) And Uehara teaches that herbimycin A reduces tyrosine phosphorylation in cells expressing ErbB. (Uehara et al., *Inhibition of*

Transforming Activity of Tyrosine Kinase Oncogenes by Herbimycin A, 164 Virology 294, 296 (1988) (Ex. 1027) ("Uehara").) A POSA would have known that EGFR is a member of the *erbB* family. (Eastman Decl. ¶150 (Ex. 1002).)

A POSA would have understood that, when added to a system in which EGFR is present (e.g., by administration to an animal or human patient, as Honma suggests), herbimycin A necessarily inhibits EGFR. (*Id.* ¶151.)

Thus, Honma's teaching to use its combination in treating leukemia in view of the general knowledge in the art regarding herbimycin A and EGFR renders this element of claim 3 obvious. (*Id.* ¶¶149-52.)

D. Claim 5

Claim 5 is also obvious over Honma in view of the knowledge of a POSA. (*Id.* ¶¶ 153-63 (Ex. 1002); *see infra* §X). Claim 5 shares many limitations with claim 2, and includes claim terms identical to those discussed in Sections VIII.A.ii, VIII.A.iii, and VIII.B.i, which are incorporated by reference here. Claim 5 differs from claim 2 in only three ways: it has a different preamble; it requires that "the agent and the inhibitor act in combination to enhance *apoptosis*," rather than "cell death"; and it has no closing "thereby" clause.

i. *"A method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention in a patient, the method comprising"*

As explained above (*see supra* §VII.A), the preamble is not limiting. However, even if Patent Owners argue it is limiting, Honma teaches a method of enhancing apoptosis (i.e., "a series of intracellular events that lead to target cell death" ('512 patent at 5:35-38 (Ex. 1001); *see also supra* §VII.D) of cancer cells in a patient. (Eastman Decl. ¶¶155-61 (Ex. 1002).)

Honma discloses that herbimycin A inhibits $p210^{c\text{-}abl}$, which is a tyrosine kinase also known as Bcr-Abl. (*See supra* §VIII.A.iv; Eastman Decl. ¶¶122-123 (Ex. 1002).) By 1994, it was well known that Bcr-Abl suppresses the intracellular events that lead to target cell death. (Eastman Decl. ¶158.) For example, it was known that the K562 cell line—the same cell line used in Honma, which expresses the Bcr-Abl tyrosine kinase—was particularly resistant to programmed cell death. (Martin et al., *Induction of Apoptosis (Programmed Cell Death) in Human Leukemic HL-60 Cells by Inhibition of RNA or Protein Synthesis*, 145 J. Immunology 1859, 1859 (1990) (Ex. 1028); *see also* Eastman Decl. ¶158.) In early 1994, McGahon disclosed that Bcr-Abl's antiapoptotic effect "is dependent on the *abl* kinase activity in [the] chimeric [Bcr-Abl] protein." (McGahon et al., *BCR-ABL Maintains Resistance of Chronic Myeloid Leukemia Cells to Apoptotic Cell Death*, 83 Blood 1179, 1179-1186 (1994) (Ex. 1029) ("McGahon"); *see also*

Bedi et al., *Inhibition of Apoptosis by BCR-ABL in Chronic Myeloid Leukemia*, 83 Blood 2038, 2038, 2043 (1994) (Ex. 1032) (showing that Bcr-Abl prolongs survival by inhibiting apoptosis in leukemia cells and suggesting that "inhibition of apoptosis by BCR-ABL may play an important role in clonal expansion, tumor progression, and resistance to cytotoxic therapy in CML"); Eastman Decl. ¶¶159-60 (Ex. 1002).).

A POSA would have understood that inhibiting Bcr-Abl's tyrosine kinase activity would suppress Bcr-Abl's antiapoptotic activity. (*See* Eastman Decl. ¶¶157-60.) For example, McGahon reported that cells expressing Bcr-Abl—K562 cells, the same cells studied in Honma—are "resistant to the induction of apoptosis by a number of [chemotherapeutic] agents," but that those same cells undergo a series of intracellular events that lead to target cell death when an inhibitor is used to reduce Bcr-Abl activity. (McGahon at 1179 (Ex. 1029); *see also* Eastman Decl. ¶¶158-59.)

It was also well known by early 1994 that chemotherapeutic drugs—many of which are DNA damaging agents—kill cancer cells by inducing them to undergo a series of intracellular events that lead to target cell death. (Eastman Decl. ¶¶95, 159-60 (Ex. 1002).) Thus, it would have been obvious to a POSA that a combination of a chemotherapeutic DNA damaging agent (which would induce apoptosis) with a Bcr-Abl tyrosine kinase inhibitor (which would suppress Bcr-

Abl's antiapoptotic effects) would enhance apoptosis. (*Id.* ¶¶157-60.) Indeed, McGahon reported that "[i]nhibition of *bcr-abl* to render [cancer] cells susceptible to apoptosis can be combined with therapeutic drugs and/or treatment capable of inducing apoptosis to provide an effective strategy for the elimination of these cells." (McGahon at 1179 (Ex. 1029); *see also* Eastman Decl. ¶159.) Since Honma disclosed just such a combination, a POSA would have understood that Honma's methods would enhance apoptosis. (Eastman Decl. ¶159-61.)

In addition, a POSA would also have understood Honma's methods to enhance apoptosis for the reasons discussed in Section VIII.A.v, above, which is incorporated by reference here.

"Chemotherapeutic intervention" and "in a patient" are addressed above, in Section VIII.A.i, which is incorporated by reference here. A POSA would therefore have understood Honma to disclose claim 5's preamble. (Eastman Decl. ¶¶154-61 (Ex. 1002).)

ii. ***"wherein the agent and the inhibitor act in combination to enhance apoptosis"***

This limitation of claim 5 requires that the agent and the inhibitor act in combination to enhance a series of intracellular events that lead to target cell death. As discussed in Section VIII.D.i, immediately above, which is incorporated by

reference here, they do. A POSA would therefore have understood Honma to disclose this limitation. (*Id.* ¶162.)

E. Claim 6

Claim 6 is also obvious over Honma in view of the knowledge of a POSA. *See infra* §X. Claim 6 shares its limitations—specifically, the limitations discussed in Sections VIII.A.i, VIII.A.ii, VIII.A.iii, and VIII.A.vi, which are incorporated by reference here—with claim 2, with two exceptions. First, where claim 2 requires that the low molecular weight inhibitor binds intracellularly "to inhibit the activity of more than one tyrosine kinase protein and intracellularly inhibits phosphorylation of downstream effector molecules," claim 6 requires that it bind intracellularly "to alter substrate function by inhibiting substrate phosphorylation" (i.e., it does not need to inhibit multiple tyrosine kinases). Second, where claim 2 requires that the agent and the inhibitor act in combination "to enhance cell death," claim 6 recites more broadly that they act in combination "to alter the cell's response to the agent." Honma discloses both limitations.

i. *"wherein the low molecular weight inhibitor binds intracellularly to alter substrate function by inhibiting substrate phosphorylation"*

Honma discloses this limitation by teaching tyrosine kinase inhibition by herbimycin A. (*See supra* §VIII.B.i; Eastman Decl. ¶¶164-65 (Ex. 1002).) The '512 specification acknowledges that "[i]nhibition of ... activation of ... tyrosine

kinases prevents or inhibits substrate phosphorylation." ('512 patent at 17:67-18:2 (Ex. 1001); *see also* Eastman Decl. ¶165.) A POSA would have understood that, as stated in the '512 patent, "[b]ecause the function of [tyrosine kinase] substrates depends on their state of phosphorylation, inhibition of phosphorylation alters the function of those substrates." ('512 patent at 18:2-4 (Ex. 10XX); Eastman Decl. ¶165 (Ex. 1002).)

ii. ***"wherein the agent and the inhibitor act in combination to alter the cell's response to the agent"***

Honma discloses that herbimycin A and Adriamycin act in combination to alter leukemia cells' response to Adriamycin. (Eastman Decl. ¶¶167-70 (Ex. 1002).)

For example, Figure 5 of Honma, titled "Enhancement by herbimycin A of antiproliferative activity of Adriamycin on K562 cells," shows that herbimycin A enhances the ability of Adriamycin to inhibit cell growth. (Honma at 333 & fig. 5 (Ex. 1003).) This figure demonstrates (1) that herbimycin A alone had almost no effect on cell number after 5 days over a dose range from 1×10^{-8} M to 5×10^{-8} M; and (2) that, at a constant concentration of Adriamycin, K562 cell numbers decreased as the concentration of herbimycin A increased. (*Id.*) Honma teaches that these results "indicate that a low concentration of herbimycin A increases inhibition of cell growth of K562 cells by Adriamycin." (*Id.* at 333.) A POSA

would have understood Figure 5 and its supporting discussion to show that herbimycin A, the inhibitor, alters the cell's response to Adriamycin, the agent, as required by this limitation of claim 6. (Eastman Decl. ¶168 (Ex. 1002).)

Further, as explained above, Honma demonstrates that the herbimycin A/ Adriamycin combination alters the cell's response to the agent in other ways. Specifically, Honma discloses that herbimycin A enhances Adriamycin's ability to induce differentiation of leukemia cells, and it would have been obvious to a POSA that the combination alters the cell's response to Adriamycin in other ways as well. (*See supra* §§VIII.A.v and VIII.D.i, which is incorporated by reference here; Eastman Decl. ¶170 (Ex. 1002).)

IX. Ground II: The Challenged Claims Are Obvious over Honma in View of the Knowledge of a POSA, Honma 1992, and McGahon.

Even if Patent Owners assert that a POSA's knowledge would have been narrower than that discussed in Ground I, the Challenged Claims are obvious over Honma in view of the knowledge of a POSA, Honma 1992, and McGahon. (Eastman Decl. ¶173-183 (Ex. 1002).) A POSA would have been motivated to combine these publications with Honma, at least because they involve administration of the same tyrosine kinase inhibitor (i.e., herbimycin A) or inhibition of the same tyrosine kinase (Bcr-Abl). The entire discussion of Ground

I above is incorporated here by reference, and additional aspects of Ground II are discussed specifically below.

A. Honma 1992 reinforces that a POSA would have had a reasonable expectation of success in administering the Honma combination "to the/in a patient."

Honma 1992, which is §102(b) art, discloses administration of herbimycin A to animals. As discussed above, a POSA would have been motivated to use Honma's combination in animals (which are "patients" as that term is used in the '512 patent) given Honma's promising results and suggestion that the combination could be used to treat leukemia, as well as the normal progression of biomedical experiments. (*See supra* §VIII.A.i, which is incorporated here by reference.) A POSA would also have had a reasonable expectation of success in administering the combination to human patients, including because Honma 1992 discloses successful administration of herbimycin A to animals and because administration of Adriamycin to humans for cancer treatment was already common practice. (Eastman Decl. ¶¶175-78 (Ex. 1002).)

B. McGahon further demonstrates that the "cell death" and "apoptosis" limitations are satisfied by Honma.

McGahon published on March 1, 1994, and thus is prior art under §102(a) given that the actual priority date for the '512 patent's claims is September 19, 1994. (*See supra* §V.D.) As discussed above, McGahon teaches that inhibition of

the Bcr-Abl tyrosine kinase renders K562 cancer cells—the same cells studied in Honma—susceptible to apoptosis caused by chemotherapeutic DNA damaging agents. (*See supra* §VIII.D.i, which is incorporated here by reference.) Because McGahon addresses the effects of inhibiting one of the same tyrosine kinase proteins that Honma discloses is inhibited by herbimycin A (i.e., $p210^{c\text{-}abl}$/Bcr-Abl), McGahon would have further informed a POSA's interpretation of Honma. (Eastman Decl. ¶¶182-83 (Ex. 1002).) A POSA thus would have understood McGahon to demonstrate that administering Honma's combination enhances apoptosis, and would have understood enhanced apoptosis to be a likely cause of the antiproliferative effects reported in Figure 5 of Honma. (*Id.*)

X. Claim Chart for Grounds I and II.

Limitation	Claims	Honma (except as noted)
A method of improving chemotherapeutic intervention in a patient, the method comprising:	1, 2, 3, 6	331, 333 *Knowledge of a POSA* Ground II:[4] Honma 1992 at 4020, tbl.2 & fig. 4

[4] Ground II, each time it appears, incorporates by reference all other citations for the same limitation.

Limitation	Claims	Honma (except as noted)
A method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention in a patient, the method comprising:	5	331-33 & figs. 3-5 *Knowledge of a POSA* Ground II: Honma 1992 at 4020, tbl.2 & fig. 4; McGahon at 1179-1186
(a) administering a DNA damaging agent to the patient;	1, 2, 3, 5, 6	331-33 & figs. 4-5 *Knowledge of a POSA*
(b) administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient,	1, 2, 3, 5, 6	331-33 & figs. 3-5 *Knowledge of a POSA* Ground II: Honma 1992 at 4020, tbl.2 & fig. 4
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein, and	1	331-33 & fig. 3 *Knowledge of a POSA*
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein and intracellularly inhibits phosphorylation of downstream effector molecules, and	2, 5	331-33 & fig. 3 *Knowledge of a POSA*
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase protein by intracellularly inhibiting phosphorylation of downstream effector molecules, and	3	331-33 & fig. 3 *Knowledge of a POSA*
wherein the low molecular weight inhibitor binds intracellularly to alter substrate function by inhibiting substrate phosphorylation, and	6	331-33 & fig. 3 *Knowledge of a POSA*

Limitation	Claims	Honma (except as noted)
wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death,	1	331-33 & figs. 3-5 *Knowledge of a POSA* Ground II: 4020, tbl.2 & fig. 4 McGahon at 1179-86
wherein the agent and the inhibitor act in combination to enhance cell death,	2, 3	331-33 & figs. 3-5 *Knowledge of a POSA* Ground II: McGahon at 1179-86
wherein the agent and the inhibitor act in combination to enhance apoptosis.	5	331-33 & figs. 3-5 *Knowledge of a POSA* Ground II: McGahon at 1179-86
wherein the agent and the inhibitor act in combination to alter the cell's response to the agent,	6	331-33 & figs. 3-5 *Knowledge of a POSA*
thereby improving chemotherapeutic intervention.	1, 2, 3, 6	331, 333 *Knowledge of a POSA* Ground II: Honma 1992 at 4020, tbl.2 & fig. 4

XI. Ground III: The Challenged Claims Are Obvious over Akinaga in View of the Knowledge of a Person of Ordinary Skill in the Art.

As explained above, September 19, 1994 is the earliest priority date to which the '512 patent's claims are actually entitled. (*See supra* §V.D.) Akinaga is therefore §102(b) art. At a minimum, Akinaga is prior art under §102(a).

Regardless of the priority date, however, the Challenged Claims are obvious over Akinaga in view of the knowledge of a POSA.

Akinaga discloses that the administration of MMC (a chemotherapeutic DNA damaging agent) with UCN-01 (a tyrosine kinase inhibitor) results in enhanced antitumor activity in cell- and animal-based cancer models. (Akinaga at 183, 188-89 & tbls.2-5 (Ex. 1004); Eastman Decl. ¶¶96-98 (Ex. 1002).) As discussed above (*see supra* §V.C), Akinaga was used in a rejection during prosecution of the '512 patent's grandparent, the '832 patent, but was distinguished on the basis that the Examiner had not established Akinaga taught a tyrosine kinase inhibitor. (9/19/2001 Decision at 5-6 (Ex. 1017).) Yet Akinaga explicitly discloses that UCN-01 inhibits "$pp60^{v\text{-}src}$," which is identified as "v-src ***tyrosine kinase***" in a table labeled "[i]nhibition of protein kinase." (Akinaga at 184 tbl.1 (Ex. 1004) (emphasis added).) The claims of the '512 patent do not require any particular level of tyrosine kinase inhibition.

Akinaga also presents a cell-cycle-based theory for combining DNA damaging agents and tyrosine kinase inhibitors—just as the '512 patent later did. Specifically, Akinaga discloses that MMC and UCN-01 both caused arrest in the cell cycle, but they did so in different phases. (*Id.* at 186-87 & fig. 4.) Hence the combination showed "a synergistic cytotoxic effect." (*Id.* at 183.) "These findings," according to Akinaga, "can be taken as a strong indication for

combining both drugs." (*Id.* at 188; *see also* Eastman Decl. ¶¶ 103-104 (Ex. 1002).) Patent Owners did not bring these statements from Akinaga to the Examiner's attention. Rather, while pursuing the '512 patent claims, they submitted a declaration from inventor Dr. Kufe containing the assertion that tyrosine kinase inhibitors were thought to interfere with DNA damaging agents. (4/16/2010 Kufe Decl. ¶5 (Ex. 1019); 4/23/2010 Resp. at 5-8 (Ex. 1020).)

Akinaga is directly relevant to this issue and, contrary to Dr. Kufe's assertion, teaches that those skilled in the art already had identified beneficial interaction between the two types of compounds based on their cell cycle effects. Further, a POSA would have known that UCN-01 satisfies the functional limitations of the Challenged Claims, and would have understood that the results Akinaga reports with the UCN-01/MMC combination demonstrate that the combination enhances cell death.

A. Claim 1

The method of claim 1 is rendered obvious by Akinaga in view of the knowledge of a POSA. (Eastman Decl. ¶¶189-216 (Ex. 1002); *see also infra* §XIII.)

i. *"A method of improving chemotherapeutic intervention in a patient, the method comprising"*

As explained above, the preamble is not limiting. (*See supra* §VII.A.) Even if Patent Owners argue that it is limiting, Akinaga teaches a method of "improving chemotherapeutic intervention." (Eastman Decl. ¶¶190-94 (Ex. 1002).)

Akinaga teaches that combining the chemotherapeutic DNA damaging agent MMC with UCN-01 results in an improved chemotherapeutic intervention over the use of MMC alone. (Akinaga at 183, 188 (Ex. 1004); *see also* Eastman Decl. ¶¶191-92.) More specifically, treatment with MMC exhibited weak but significant antitumor activity in xenografted A431 tumors in nude mice, but when used together, UCN-01 and MMC achieved a minimum treated vs. control (T/C) tumor volume of less than 0.5 at all doses examined. (Akinaga at 186-87 & tbl. 2 (Ex. 1004).)

These data establish an improvement in chemotherapeutic intervention because they show significant growth inhibition from the combination of UCN-01 and MMC. (Eastman Decl. ¶192 (Ex. 1002).) Indeed, Akinaga discloses that UCN-01 and MMC exert "an additive cytostatic effect and a synergistic cytotoxic effect" on cancer cells. (Akinaga at 186 (Ex. 1004); *see also id.* at 188 ("UCN-01 potentiated the antiproliferative activity of MMC").) A POSA would have understood "cytotoxic" to refer to toxicity that kills cells. (Stenesh, Dictionary of

Biochemistry and Molecular Biology 115 (2d. ed. 1989) (defining "cytotoxicity" as "causing cell death") (Ex. 1030); Eastman Decl. ¶¶95, 211 (Ex. 1002).) Thus, Akinaga discloses that UCN-01 improves the chemotherapeutic intervention of MMC. (Eastman Decl. ¶¶190-92.)

Akinaga also discloses improved chemotherapeutic intervention "in a patient." Akinaga teaches that there are measurable added effects from the combination of UCN-01 with MMC over the use of MMC alone in four *in vivo* animal (mouse) models: the human epidermoid carcinoma A431 xenograft model, the human colon carcinoma Co-3 xenograft model, the sarcoma 180 model, and the P388 leukemia model. (Akinaga at 186-88 & tbls.2-5 (Ex. 1004); *see also* Eastman Decl. ¶¶100-01, 190-93, 204-05 (Ex. 1002).) In the three solid tumor models, Akinaga compares tumor volume in treated vs. control populations and reports greater growth inhibition from the combination of MMC and UCN-01 than treatment with either agent alone. (Akinaga at 186-87 & tbls.2-4; Eastman Decl. ¶¶101-02, 191-92, 215.) The leukemia model shows that the combination increased mean survival. (Akinaga at 188 & tbl.5 (Ex. 1004).)

Akinaga further suggests the use of UCN-01 and MMC in human patients in a clinical setting. (*Id.* at 183 ("These results suggests the feasibility of using UCN-01 in clinical oncology, especially in combination with alkylating agents such as MMC."); *id.* at 189 ("[T]he results of our *in vivo* studies strongly suggest that this

novel combination chemotherapy may merit clinical trials in cancer patients."); *see also* Eastman Decl. ¶¶193-94 (Ex. 1002).) Accordingly, to the extent the preamble is deemed to be limiting, Akinaga discloses it.

ii. *"administering a chemotherapeutic DNA damaging agent to the patient"*

Akinaga discloses administering a chemotherapeutic DNA damaging agent. More specifically, Akinaga teaches the administration of the alkylating agent MMC, which was well known to be a cancer chemotherapeutic. (Akinaga at 183 (Ex. 1004); Eastman Decl. ¶¶195-97.) The '512 patent itself notes that MMC is a chemotherapeutic DNA damaging agent. ('512 patent at 4:46-51 (Ex. 1001) ("Chemotherapeutic agents contemplated to be of use, include, e.g., mitomycin C (MMC)"); *id.* at 18:35-41.)

Administration to a patient is discussed above, *see supra* §XI.A.i, and incorporated by reference here.

iii. *"administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient"*

Akinaga teaches administering a tyrosine kinase inhibitor. Akinaga discloses that administration of UCN-01 inhibits "$pp60^{v\text{-}src}$," which is identified as "v-src tyrosine kinase" in a table labeled "[i]nhibition of protein kinase." (Akinaga at 184 & tbl.1 (Ex. 1004).) Src kinases make up one of the families of kinases explicitly referenced in the '512 patent. ('512 patent at 2:27-29 (Ex.

1001); *id.* at 19:13-14.) The human homologue of v-Src is c-Src, which UCN-01 necessarily inhibits by the same mechanism as it inhibits v-Src. (Eastman Decl. ¶¶199-202 (Ex. 1002); Robinson et al., *Enzyme, Whole Cell and In vivo Tumor-Models to Identify and Assess Inhibitors of pp60(c-src)*, 2 Int'l J. Oncology 253, 255 (1993) (Ex. 1036).)

UCN-01 is a low molecular weight inhibitor because it has a molecular weight of 482.53 daltons. (Eastman Decl. ¶203 (Ex. 1002).) As noted above (*see supra* §VIII.A.iii), small molecules (i.e., low molecular weight compounds) are typically understood to have a molecular weight of less than 900 daltons. (Eastman Decl. ¶203.)

Akinaga discloses administering a therapeutically effective amount of UCN-01. Akinaga teaches concentrations of UCN-01 that produce desired effects in *in vitro* studies, as it enhances the antiproliferative effects of MMC in A431 human epidermoid carcinoma cells. (Akinaga at 184-86 & figs. 2-3 (Ex. 1004); Eastman Decl. ¶204 (Ex. 1002).) Although this limitation does not require evidence of *in vivo* therapeutic effect, Akinaga also discloses *in vivo* dosing and efficacy data for UCN-01. (Akinaga at 186-88 & tbls.2-5 (reporting antitumor effect of combination in four different mouse models); Eastman Decl. ¶204.)

Administration to a patient is discussed above, (*see supra* §XI.A.i), and incorporated by reference here.

iv. *"wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein"*

UCN-01 inhibits Src, which is an intracellular tyrosine kinase protein. (Eastman Decl. ¶¶98, 199-200 (Ex. 1002).) Indeed, a POSA would have understood that UCN-01 inhibits the phosphorylation of "discrete ***cellular*** proteins." (Seynaeve at 2085 (Ex. 1014) (emphasis added); Eastman Decl. ¶¶207-08, 244.) Thus, UCN-01 must enter the cell and affect the activity of kinases intracellularly. (Eastman Decl. ¶207.) Patent Owners admitted as much during prosecution of the '512 patent when they argued that low molecular weight tyrosine kinase inhibitors—unlike MAbs—"exert their effects intracellularly by intracellular binding." (9/11/2009 Resp. at 8 (Ex. 1025).)

A POSA would have known that UCN-01 inhibits more than one tyrosine kinase because, by 1993, it had been established that UCN-01 "decreases tyrosine phosphorylation of at least 4 proteins." (Seynaeve at 2084-85 (Ex. 1014); Eastman Decl. ¶208 (Ex. 1002).) This decreased tyrosine phosphorylation reflects decreased tyrosine kinase activity, not all of which can be accounted for by Src inhibition. (Eastman Decl. ¶208.) As discussed in further detail below, UCN-01 also inhibits the activity of EGFR. (*See infra* §XI.C.)

Accordingly, Akinaga discloses that UCN-01 "binds intracellularly to inhibit the activity of more than one tyrosine kinase protein."

v. *"wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death"*

Akinaga discloses that MMC and UCN-01 "act in combination by effecting a series of intracellular events to enhance cell death." Specifically, Akinaga presents isobologram analysis (i.e., a technique for analyzing combination therapies) for the combination of MMC and UCN-01 at IC_{80} concentrations and teaches that the combination has a synergistic cytotoxic (i.e., cell killing) effect. (Akinaga at 185-86, 188 & fig.3B (Ex. 1004); *see also* Eastman Decl. ¶¶99, 211 (Ex. 1002) (discussing definition of "cytotoxicity").) Akinaga ties the synergistic cytotoxic effects achieved by the combination to particular intracellular events involved in the cell cycle. (Akinaga at 186-88 & fig. 4 (Ex. 1004) (comparing impact on cell cycle between treatment with MMC alone (block at G_2/M) and treatment with MMC and UCN-01 (S phase prolongation).) Akinaga's cytotoxic results and cell cycle observations are consistent with what had previously been reported by others, including Lau (Ex. 1013) and Tam (Ex. 1012)—namely, that causing cells with damaged DNA to undergo mitosis rather than being permitted to repair their DNA leads to cell death. (Eastman Decl. ¶¶212-13.) Accordingly, a POSA would have understood these disclosures of Akinaga to demonstrate that the MMC/UNC-01 combination enhances cell death. (*Id.* ¶¶210-14.)

vi. *"thereby improving chemotherapeutic intervention"*

As explained above, "thereby improving chemotherapeutic intervention" is a non-limiting statement of intended result. (*See supra* §§VII.E, VIII.A.vi.) But, as also discussed above, if this clause is deemed limiting, Akinaga discloses it. (*See supra* §XI.A.i.)

B. Claim 2

Akinaga also renders obvious claim 2. (Eastman Decl. ¶¶217-19 (Ex. 1002); *see also infra* §XII.) As noted above, claim 2 includes claim elements identical to those discussed in Sections XI.A.i, XI.A.ii, XI.A.iii, and XI.A.vi, which are incorporated by reference here. Claim 2 does not require that "the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death," but merely that they "act in combination to enhance cell death." Because Akinaga renders obvious the narrower form of this limitation in claim 1, as explained above in Section XI.A.v, which is also incorporated by reference here, it also renders obvious the broader form in claim 2. (*See* Eastman Decl. ¶217 (Ex. 1002).) The only other difference between claim 1 and claim 2 is addressed immediately below.

i. *"wherein the low molecular weight inhibitor ... intracellularly inhibits phosphorylation of downstream effector molecules"*

As discussed above, UCN-01 intracellularly inhibits Src, among other kinases. (*See supra* §XI.A.iv.) Indeed, UCN-01 was found to "decrease[] tyrosine phosphorylation of at least 4 proteins." (Seynaeve at 2085 (Ex. 1014); *see also* Eastman Decl. ¶¶207-08, 218 (Ex. 1002).) The specification of the '512 patent also says that "[i]nhibition of ... activation of ... tyrosine kinases prevents or inhibits substrate phosphorylation." ('512 patent at 17:67-18:2 (Ex. 1001); *see also* Eastman Decl. ¶218.) A POSA would have understood that a substrate is a downstream effector molecule of a tyrosine kinase protein. (Eastman Decl. ¶218.) A POSA also would have understood that, following activation of a tyrosine kinase protein, each of the steps in the signal transduction pathway proceeds through phosphorylation of downstream effector molecules (i.e., molecules downstream from the tyrosine kinase protein in the pathway). (*Id.* ¶218.) If the tyrosine kinase is inhibited, signal transduction along the pathway is also inhibited. (*Id.* ¶218.) Therefore, a POSA would have understood Akinaga to necessarily disclose the intracellular inhibition of phosphorylation of downstream effector molecules. (*Id.* ¶¶217-19.)

C. Claim 3

Akinaga also renders obvious the method of claim 3. (*Id.* ¶220-26; *see also infra* §XII.) Claim 3 is very similar to claim 2. As discussed above (*see supra* §VIII.C), the key distinction between the claims is that claim 3 requires the tyrosine kinase inhibitor to *inhibit the activity of EGFR* and at least one other tyrosine kinase protein.

i. *"wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase protein"*

A POSA would have known that administration of UCN-01 would inhibit the activity of EGFR. (Akinaga et al., *Antitumor Activity of UCN-01, a Selective Inhibitor of Protein Kinase C, in Murine and Human Tumor Models*, 51 Cancer Res. 4888, 4889-90 & fig. 2 (1991) (Ex. 1035) ("Akinaga 1991"); Eastman Decl. ¶¶223-25 (Ex. 1002).) Akinaga 1991 suggests that UCN-01 inhibits EGFR down-modulation, which is an aspect of EGFR activity. (Akinaga 1991 at 4889-90 & fig. 2 (Ex. 1035).)

Furthermore, staurosporine (a close structural analog of UCN-01, which is 7-hydoxystaurosporine) was known to inhibit Src (like UCN-01) and also EGFR. (*See* Tam at 811 (Ex. (1012) ("[s]taurosporine is a potent general protein kinase inhibitor that can suppress in vitro the activity of ... the tyrosine kinases $p60^{v\text{-}src}$ and epidermal growth factor receptor"); Eastman Decl. ¶224 (Ex. 1002).) Like

UCN-01, staurosporine was also found to inhibit EGFR down-modulation. (*Compare* Akinaga 1991 at 4889-90 & fig. 2 (Ex. 1035), *with* Friedman at 537-38 & fig. 8 (Ex. 1031); Eastman Decl. ¶224 (Ex. 1002).) Indeed, staurosporine and its analogs were known to inhibit kinase activity in the same way—competition with ATP at the ATP binding domain of a kinase. (Friedman at 538 (Ex. 1031); Eastman Decl. ¶224.) Based on this mechanism of action, a POSA would have logically predicted that UCN-01 would also inhibit the tyrosine kinase activity of EGFR. (Eastman Decl. ¶225.)

Thus, a POSA would have understood that UCN-01 "inhibit[s] the activity of EGFR and at least one other tyrosine kinase protein" (i.e., Src). (*Id.* ¶225; *see supra* §XI.A.iv, which is incorporated by reference here.)

D. Claim 5

Akinaga also renders the method of claim 5 obvious. (Eastman Decl. ¶¶227-33 (Ex. 1002); *see also infra* §XII.) Claim 5 shares many limitations with claim 2, and includes claim terms identical to those discussed in Sections XI.A.ii, XI.A.iii, XI.B.i, and XI.A.iv, which are incorporated by reference here. Claim 5 differs from claim 2 in that it has a different preamble; it requires that "the agent and the inhibitor act in combination to enhance *apoptosis*," rather than "cell death"; and it has no closing "thereby" clause. The apoptosis limitations are discussed below.

i. *"A method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention in a patient, the method comprising"*

As explained above, the preamble of claim 5 is not limiting. (*See supra* §§VII.A, VIII.D.i.) But even if Patent Owners argue that it is limiting, Akinaga teaches "a method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention." (Eastman Decl. ¶¶228-30 (Ex. 1002).)

Akinaga discloses that "UCN-01 and MMC exert an additive cytostatic effect and a synergistic cytotoxic [i.e., cell-killing] effect" in an *in vitro* model, and "synergistic antitumor effects" in *in vivo* models. (Akinaga at 183, 185 fig. 2, 186-88 tbls.2-5 (Ex. 1004).) UCN-01, in particular, causes cell cycle events that contribute to these results. (*Id.* at 186 & fig. 4; Eastman Decl. ¶229 (Ex. 1002).) Akinaga discloses that MMC alone blocked the cell cycle at a particular phase (the G_2/M phase), while the combination removed or prevented this block and instead caused prolongation of a different phase of the cell cycle (the S phase). (Akinaga at 186-87 & fig. 4 (Ex. 1004); *see also* Eastman Decl. ¶229.) A POSA would have understood that by affecting the cell cycle in this way, the combination results in apoptosis. (*See supra* §VII.D (defining apoptosis as "a series of intracellular events that lead to target cell death"); Eastman Decl. ¶229.)

In particular, a POSA would have understood that inducing cells with damaged DNA to "undergo mitosis before properly repairing lesions in their

DNA" (Eastman Decl. ¶229 (Ex. 1002) (citing Lau at 2942 (Ex. 1013))), leads to micronucleation of cells, a condition from which the cells will not recover. (Eastman Decl. ¶229 (Ex. 1002) (citing Tam (Ex. 1012).) As a result, the cells undergo apoptosis. (*Id.*) Thus, a POSA would have understood Akinaga to disclose that UCN-01 "potentiates the lethality" of the chemotherapeutic DNA damaging agent MMC, thereby enhancing apoptosis. (*Id.* (citing Lau, Tam).)

Administration to a patient is discussed above, *see supra* §XI.A.i, and incorporated by reference here.

ii. *"wherein the agent and the inhibitor act in combination to enhance apoptosis"*

For the same reasons as discussed immediately above, Akinaga discloses "wherein the agent and the inhibitor act in combination to enhance apoptosis." (*See supra* §XI.D.i, incorporated here by reference; *see also* Eastman Decl. ¶¶231-32 (Ex. 1002).)

E. Claim 6

Akinaga also renders obvious the method of claim 6. (Eastman Decl. ¶¶234-40 (Ex. 1002); *see also infra* §XII.) As noted above, claim 6 shares many limitations with claim 2, but is even broader because it requires the inhibition of only one tyrosine kinase. The two differences between claims 2 and 6—both of which Akinaga discloses—are addressed immediately below. Claim 6's remaining

limitations are discussed in Sections XI.A.i, XI.A.ii, XI.A.iii, XI.A.vi, which are incorporated by reference here.

i. *"wherein the low molecular weight inhibitor binds intracellularly to alter substrate function by inhibiting substrate phosphorylation"*

As discussed above, UCN-01 inhibits Src, among other kinases, (Akinaga at 184 & tbl.1; *see supra* §§XI.A.iv, XI.C), and therefore inhibits the phosphorylation of those kinases' target substrates. (Eastman Decl. ¶¶235-37 (Ex. 1002).) Indeed, UCN-01 was found to "decrease[] tyrosine phosphorylation of at least 4 proteins." (Seynaeve at 2085 (Ex. 1014); *see also* Eastman Decl. ¶236.) The phosphorylation state of a substrate affects its function, so inhibiting a substrate's phosphorylation necessarily alters the function of the substrate. (Eastman Decl. ¶236;'512 patent at 18:2-4 (Ex. 1001).) Accordingly, Akinaga discloses this limitation. (Eastman Decl. ¶237.)

ii. *"wherein the agent and the inhibitor act in combination to alter the cell's response to the agent"*

Akinaga discloses that MMC and UCN-01 act in combination to alter the cell's response to MMC. Akinaga discloses that "UCN-01 potentiated the antiproliferative activity of MMC at a concentration as low as 50 nM." (Akinaga at 188 (Ex. 1004).) Akinaga also teaches that, when administered in combination, UCN-01 and MMC have an additive cytostatic effect and a synergistic cytotoxic effect. (*Id.* at 186, 188.)

Furthermore, the combination alters the effect of MMC on the cell cycle. According to Akinaga, MMC alone blocked the cell cycle at the G_2/M phase at 48 hours, while the combination removed or prevented this block and instead caused prolongation of a different phase of the cell cycle (the S phase). (*Id.* at 186-87 & fig. 4 (Ex. 1004); *see also* Eastman Decl. ¶239 (Ex. 1002).)

XII. Ground IV: The Challenged Claims Are Obvious over Akinaga in View of the Knowledge of a POSA, Seynaeve, Tam, and Friedman.

Even if Patent Owners assert that the knowledge of a POSA is narrower than that discussed in Ground III, the Challenged Claims are obvious over Akinaga in view of the knowledge of a POSA, Seynaeve, Tam, and Friedman. A POSA would have been motivated to combine each of these publications with Akinaga, at least because they involve administration of the same tyrosine kinase inhibitor (UCN-01) or its close structural analog, which has substantially similar effects on the cell cycle. The entire discussion of Ground III above is incorporated here by reference, and additional aspects of Ground IV are discussed specifically below.

A. Seynaeve reinforces that UCN-01 inhibits multiple tyrosine kinases.

Seynaeve published on May 1, 1993 and is therefore prior art under §102(b) given that the earliest priority date to which the '512 patent's claims are actually entitled is September 19, 1994. (*See supra* §V.D.) At a minimum, Seynaeve is prior art under §102(a). As discussed above, Seynaeve teaches that administration

of UCN-01 "decreased tyrosine phosphorylation of at least 4 proteins." (*See supra* §XI.A.iv.) Seynaeve further discloses that UCN-01's effect on the cell cycle "correlates with the persistent inhibition of ... tyrosine phosphorylation of discrete cellular phosphoproteins." (Seynaeve at 2081 (Ex. 1014); Eastman Decl. ¶244 (Ex. 1002).) These disclosures would have informed a POSA's understanding that UCN-01 is not only a tyrosine kinase inhibitor, but that it inhibits multiple tyrosine kinases. (Eastman Decl. ¶245.)

B. In view of Tam and Friedman, a POSA would have understood that administering UCN-01 inhibits EGFR, and when administered in combination with MMC causes a series of intracellular events that lead to target cell death.

Tam, which published in 1992 and is prior art under §102(b), discloses administration of staurosporine—a close structural analog of UCN-01—in combination with the chemotherapeutic DNA damaging agent hydroxyurea. (*Id.* ¶248 (explaining UCN-01 is 7-hydroxy-staurosporine) (Ex. 1002).) Like UCN-01, Tam discloses that staurosporine inhibits "the tyrosine kinases $p60^{v\text{-}src}$ and epidermal growth factor receptor." (Tam at 811 (Ex. 1012); Eastman Decl. ¶248.) Tam teaches that "staurosporine bypasses normal checkpoints for mitotic onset" and "induces premature mitosis in cells that contain incompletely replicated genomes and suppresses G_2 delay in cells that have suffered DNA damage." (Tam at 811 (Ex. 1012).) Figure 1 in Tam demonstrates that this results in a series of

intracellular events that lead to target cell death. (*Id.* at 811-12 & fig. 1; Eastman Decl. ¶¶248-49 (Ex. 1002).) The cells arrest in S phase and then bypass the G_2 phase, directly entering mitosis. (Tam at 815-16 (Ex. 1012); Eastman Decl. ¶249 (Ex. 1002).) These intracellular events lead to micronucleation of the cells, causing a condition from which the cells will not recover, and a POSA would have understood the cells would die as a result. (Eastman Decl. ¶249 (Ex. 1002).)

Similarly, Akinaga discloses cell cycle data showing that the combination of UCN-01 and MMC cause S phase prolongation, but none of the DNA damage induced accumulation in the G_2 phase that was seen when administering MMC alone. (Akinaga at 187-87 & fig. 4 (Ex. 1004); Eastman Decl. ¶247 (Ex. 1002).) In view of Tam, a POSA would have understood these cell cycle data to be evidence that UCN-01 causes premature mitosis in cells with DNA damage caused by MMC. (Eastman Decl. ¶250.) Thus, a POSA would have understood that administering UCN-01 in combination with MMC causes a series of intracellular events that lead to target cell death. (*Id.* ¶246.)

Friedman published in 1990 and is also prior art under §102(b). Friedman teaches that staurosporine inhibits the activity of EGFR, and does so by interfering with ATP binding. (*See supra* §XI.C; Eastman Decl. ¶251 (Ex. 1002).) Because staurosporine and UCN-01 operate by the same mechanism and affect EGFR

down-modulation similarly, a POSA would have understood that UCN-01 also inhibits EGFR tyrosine kinase activity. (Eastman Decl. ¶251.)

XIII. Claim Chart for Grounds III and IV

Limitation	Claims	Akinaga (except as noted)
A method of improving chemotherapeutic intervention in a patient, the method comprising:	1, 2, 3, 6	183, 185-189, Tables 2-5, Figs. 2-3 *Knowledge of a POSA*
A method of enhancing apoptosis of cancer cells in a patient comprising chemotherapeutic intervention in a patient, the method comprising:	5	183, 185-189, Tables 2-5, Figs. 2-4 *Knowledge of a POSA* Ground IV:[5] Tam at fig. 1, 811, 812, 816
(a) administering a DNA damaging agent to the patient;	1, 2, 3, 5, 6	183, 186-189, Tables 2-5 *Knowledge of a POSA*
(b) administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient,	1, 2, 3, 5, 6	183-188, Tables 1-5, Figs. 2-3 *Knowledge of a POSA* Ground IV: Seynaeve at 2081, 2084-2085, fig. 7, Friedman at 537-38

[5] Ground IV, each time it appears, incorporates by reference all Akinaga citations for the same limitation.

Limitation	Claims	Akinaga (except as noted)
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein, and	1	183, 186-188, Tables 1-5, Figs. 2-3 *Knowledge of a POSA* Ground IV: Seynaeve at 2081, 2084-2085, fig. 7, Friedman at 537-38
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein and intracellularly inhibits phosphorylation of downstream effector molecules, and	2, 5	183, 186-188, Tables 1-5, Figs. 2-3 *Knowledge of a POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811, Friedman at Figs.7- 8, 537-538, Seynaeve at 2081, 2084-2085, fig. 7
wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase protein by intracellularly inhibiting phosphorylation of downstream effector molecules, and	3	183, 186-188, Tables 1-5, Figs. 2-3 *Knowledge of POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811-812, Friedman at Figs.7-8, 537-538, Seynaeve at 2081, 2084-2085
wherein the low molecular weight inhibitor binds intracellularly to alter substrate function by inhibiting substrate phosphorylation, and	6	183-184, 186, Fig. 2, Table 1 *Knowledge of a POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811-812, Friedman at Figs. 7-8, 537-538, Seynaeve at 2081, 2084-2085, Figs. 6-7

Limitation	Claims	Akinaga (except as noted)
wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death,	1	183, 185-188, Tables 2-5, Figs. 2-4 *Knowledge of a POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811-812, 815-816, Fig. 1, Friedman at Figs.7- 8, 538, Seynaeve at 2084-2085
wherein the agent and the inhibitor act in combination to enhance cell death,	2, 3	183-188, Tables 2-5, Figs. 2-4 *Knowledge of a POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811-812, Fig. 1, Friedman at Figs.7- 8, 538, Seynaeve at 2084-2085
wherein the agent and the inhibitor act in combination to enhance apoptosis.	5	183, 185-189, Tables 2-5, Figs. 2-4 *Knowledge of a POSA* Ground IV: Tam at fig. 1, 811, 812, 816
wherein the agent and the inhibitor act in combination to alter the cell's response to the agent,	6	183, 185-189, Tables 2-5, Figs. 2-4 *Knowledge of a POSA* Ground IV: Akinaga 1991 at 4888-4890, Fig. 2, Tam at 811-812, Fig. 1, Friedman at Figs.7- 8, 538, Seynaeve at 2081, 2084-2085

Limitation	Claims	Akinaga (except as noted)
thereby improving chemotherapeutic intervention.	1, 2, 3, 6	183, 186-189, Tables 2-5, Figs. 2-3 *Knowledge of a POSA*

XIV. Secondary Considerations of Nonobviousness Do Not Negate the Above Obviousness Grounds.

Any attempt by Patent Owners to rely on alleged secondary considerations of nonobviousness cannot overcome the showing of obviousness detailed above. Where, as here, there is a strong showing of obviousness, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence may not dislodge the primary conclusion of obviousness. *See, e.g.*, *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011). In any event, Patent Owners cannot satisfy their burden of demonstrating a nexus between any alleged secondary consideration and the alleged invention of the '512 patent. *Cf. Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013). This is especially true given that the claims broadly recite combining ***any*** low molecular weight tyrosine kinase inhibitor with ***any*** chemotherapeutic DNA damaging agent.

XV. The Grounds in This Petition Are Not Redundant.

Grounds I, II, III, and IV are independent of and not redundant of each other. Grounds I & II rely on a different primary reference than Grounds III & IV, and

Grounds II and IV specify additional references in combination. For example, Honma and Akinaga combine different tyrosine kinase inhibitors and different chemotherapeutic DNA damaging agents, and report results from different experiments carried out to assess the effects of the combinations.

XVI. Conclusion

Based on the foregoing, there is a reasonable likelihood that claims 1-3 and 5-6 of the '512 patent are unpatentable as obvious. Petitioners request institution of an *inter partes* review to cancel those claims.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a)(1)(i) because, according to the "word count" function of Microsoft Word 2010, the Petition contains 13,924 words, excluding the parts of the Petition exempted from the word count by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

I hereby certify that, on May 13, 2016, I caused a true and correct copy of the following materials:

- Petition for *Inter Partes* Review of U.S. Patent No. 7,838,512
- Exhibits 1001-1036
- Fee Authorization Page
- OSI Power of Attorney
- Genentech Power of Attorney

to be served via Express Mail on the following attorney of record as listed on PAIR:

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A courtesy copy of this Petition and supporting material was also served upon litigation counsel for Patent Owner via email:

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Petitioners' Appendix of Exhibits

Pet'rs' Ex. No.	Description
1001.	U.S. Patent No. 7,838,512
1002.	Eastman Decl.
1003.	Honma et al., *Induction of Erythroid Differentiation of K562 Human Leukemic Cells by Herbimycin A, an Inhibitor of Tyrosine Kinase Activity*, 49 Cancer Res. 331 (1989)
1004.	Akinaga et al., *Enhancement of Antitumor Activity of Mitomycin C In Vitro and In Vivo by UCN-01, a Selective Inhibitor of Protein Kinase C*, 32 Cancer Chemotherapy & Pharmacology 183 (1993)
1005.	Omura et al., *Herbimycin, a New Antibiotic Produced by a Strain of Streptomyces*, 32 J. Antibiotics 255 (1979)
1006.	Takahashi et al., *UCN-01, a Selective Inhibitor of Protein Kinase C from Streptomyces*, 40 J. Antibiotics 1782 (1987)
1007.	Gazit et al., *Tyrphostins I: Synthesis and Biological Activity of Protein Tyrosine Kinase Inhibitors*, 32 J. Medicinal Chemistry 2344 (1989)
1008.	Umezawa et al., *Studies on a New Epidermal Growth Factor-Receptor Kinase Inhibitor, Erbstatin, Produced by MH435-hF3*, 39 J. Antibiotics 170 (1986)
1009.	Fan et al., *Antitumor Effect of Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies Plus Cis-Diamminedichloroplatinum on Well Established A431 Cell Xenografts*, 52 Cancer Res. 4637 (1993)
1010.	Monti et al., *Antiproliferative Effects of Genistein and Doxorubicin Against ER-Positive and -Negative Human Breast Cancer Cell Lines*, 33 Proc. Am. Assoc. Cancer Res. 442 (1992)

Pet'rs' Ex. No.	Description
1011.	Yoneda et al., *The Antiproliferative Effects of Tyrosine Kinase Inhibitors Tyrphostins on a Human Squamous Cell Carcinoma In Vitro and in Nude Mice*, 51 Cancer Res. 4430 (1991)
1012.	Tam et al., *Staurosporine Overrides Checkpoints for Mitotic Onset in BHK Cells*, 3 Cell Growth & Differentiation 811 (1992)
1013.	Lau et al., *Mechanism by Which Caffeine Potentiates Lethality of Nitrogen Mustard*, 79 Proc. Nat'l Acad. Sci. 2942 (1982)
1014.	Seynaeve et al., *Cell Cycle Arrest and Growth Inhibition by the Protein Kinase Antagonist UCN-01 in Human Breast Carcinoma Cells*, 53 Cancer Res. 2081 (1993)
1015.	U.S. Patent No. 6,524,832
1016.	Nov. 13, 1995 Amendment and Response to Office Action, File History of U.S. Patent No. 6,524,832
1017.	Sept. 19, 2001 Decision on Appeal, File History of U.S. Patent No. 6,524,832
1018.	Jan. 4, 2010 Office Action, File History of U.S. Patent No. 7,838,512
1019.	Apr. 16, 2010 Declaration of Donald Kufe Under 37 C.F.R. §1.132, File History of U.S. Patent No. 7,838,512
1020.	Apr. 23, 2010 Response to Office Action, File History of U.S. Patent No. 7,838,512
1021.	Redline Comparison of U.S. Patent Application No. 08/309,315, as Originally Filed on September 19, 1994, to U.S. Patent Application No. 08/192,107, as Originally Filed on Feb. 4, 1994

Pet'rs' Ex. No.	Description
1022.	Honma et al., *Herbimycin A, an Inhibitor of Tyrosine Kinase, Prolongs Survival of Mice Inoculated with Myeloid Leukemia C1 Cells with High Expression of v*-abl *Tyrosine Kinase*, 52 Cancer Res. 4017 (1992)
1023.	Doxorubicin, *in* Physicians' Desk Reference 832 (45th ed. 1991)
1024.	Furusaki et al., *Herbimycin A: An Ansamycin Antibiotic; X-ray Crystal Structure*, 33 J. Antibiotics 781 (1980)
1025.	Sept. 11, 2009 Response to Advisory Action, File History of U.S. Patent No. 7,838,512
1026.	Nov. 21, 1995 Declaration of Ralph Weichselbaum Under 37 C.F.R. §1.132, File History of U.S. Patent No. 6,524,832
1027.	Uehara et al., *Inhibition of Transforming Activity of Tyrosine Kinase Oncogenes by Herbimycin A*, 164 Virology 294 (1988)
1028.	Martin et al., *Induction of Apoptosis (Programmed Cell Death) in Human Leukemic HL-60 Cells by Inhibition of RNA or Protein Synthesis*, 145 J. Immunology 1859 (1990)
1029.	McGahon et al., *BCR-ABL Maintains Resistance of Chronic Myelogenous Leukemia Cells to Apoptotic Cell Death*, 83 Blood 1179 (1994)
1030.	Stenesh, Dictionary of Biochemistry and Molecular Biology 115 (2d. ed. 1989)
1031.	Friedman et al., *Regulation of the Epidermal Growth Factor Receptor by Growth-Modulating Agents: Effects of Staurosporine, a Protein Kinase Inhibitor*, 50 Cancer Research 533 (1990)
1032.	Bedi et al., *Inhibition of Apoptosis by BCR-ABL in Chronic Myeloid Leukemia*, 83 Blood 2038 (1994)

Pet'rs' Ex. No.	Description
1033.	Oct. 2, 2006 Information Disclosure Statement, File History of U.S. Patent No. 7,838,512
1034.	Skladanowski et al., *Adriamycin and Daunomycin Induce Programmed Cell Death (Apoptosis) in Tumour Cells*, 46 Biochemical Pharmacology 375 (1993)
1035.	Akinaga et al., *Antitumor Activity of UCN-01, a Selective Inhibitor of Protein Kinase C, in Murine and Human Tumor Models*, 51 Cancer Res. 4888 (1991)
1036.	Robinson et al., *Enzyme, Whole Cell and In vivo Tumor-Models to Identify and Assess Inhibitors of pp60(c-src)*, 2 Int'l J. Oncology 253 (1993)