

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OSI PHARMACEUTICALS, LLC,
and GENENTECH, INC.,

Petitioner,

v.

ARCH DEVELOPMENT CORP. and
DANA-FARBER CANCER INSTITUTE, INC.,

Patent Owner.

Case IPR2016-01034
Patent 7,838,512 B1

Before MICHAEL P. TIERNEY, LORA M. GREEN, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

OSI Pharmaceuticals, LLC, and Genentech, Inc., (“Petitioner”)¹ filed a Petition requesting an *inter partes* review of claims 1–3, 5, and 6 of U.S. Patent No. 7,838,512 B1 (Ex. 1001, “the ’512 patent”). Paper 3 (“Pet.”). Arch Development Corp. and Dana-Farber Cancer Center Institute, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”).

Institution of an *inter partes* review is authorized by statute when “the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we institute an *inter partes* review of claims 1–3, 5, and 6 of the ’512 patent.

A. *Related Proceedings*

The ’512 Patent is at issue in *Arch Development Corp. et al. v. Genentech, Inc. et al.*, No. 1:15-cv-6597 (N.D. Ill.). Pet. 4; Paper 6.

B. *The ’512 Patent and Relevant Background*

The ’512 patent is directed to the use of DNA damaging agents in combination with tyrosine kinase inhibitors to enhance cancer cell death. *See generally*, Ex. 1001, Title, Abstract, 4:12–40, 5:28–38. According to the

¹ Petitioner further identifies Astellas US LLC, Astellas US Holding, Inc., Astellas Pharma Inc., and Roche Holdings, Inc. as real-parties-in-interest. Pet. 4

Specification, the treatment of cancer cells with ionizing radiation and some chemotherapeutic agents such as the DNA alkylating agent, mitomycin C, result in DNA damage. *Id.* at 1:32–25; 3:51–65; 4:41–54. “The cellular response to DNA damage includes activation of DNA repair, cell cycle arrest, and lethality.” *Id.* at 1:32–35 (citation omitted).

The cell cycle may be defined as four phases: G₁ (growth phase); S (DNA synthesis resulting in chromosomal duplication); G₂ (a second growth phase); and M (mitosis/cell division). *See* Ex. 1002 ¶ 40–41. Cell cycle arrest refers to the prolongation of a phase of the cell cycle, providing a checkpoint responsive to diverse positive and negative regulatory signals. Ex. 1001 at 1:38–42; Ex. 1002 ¶¶ 42–43. The Specification points to prior art studies showing that environmental conditions following exposure to DNA damaging agents can influence cell survival. Ex. 1001 1:38–55, 2:50–63. For example,

cell survival can be increased if the cells are arrested in the cell cycle for a protracted period of time following radiation exposure, allowing repair of DNA damage. (Hall, 1988). Thus [potentially lethal damage] is repaired and the fraction of cells surviving a given dose of x-rays is increased if . . . cells do not have to undergo mitosis while their chromosomes are damaged.”

Id. at 2:56–63.

The Specification focuses on G₂ arrest as “necessary for repair of DNA damage before entry into mitosis.” Ex. 1001 at 1:42–44 (citations omitted); *see id.* at 3:43–46. In particular, “[c]ells that are irradiated or treated with DNA damaging agents halt in the cell cycle at G₂, so that an inventory of chromosome damage can be taken and repair initiated and completed before mitosis is initiated.” *Id.* at 3:3–7. “By preventing delays

in G₂, cells will enter mitosis before the DNA is repaired and therefore the daughter cells will likely die.” *Id.* at 3:46–48.

Recognizing that DNA damaging agents result in the activation of p56/p53^{lyn} tyrosine kinase, a protein implicated in cell cycle control,² the Specification proposes that tyrosine kinase inhibitors generally (e.g., genistein or herbimycin A) could force damaged cells to override the G₂ arrest checkpoint and enter mitosis before completing DNA repairs, and thereby enhance cell killing. *Id.* at 3:38–42, 5:28–32; 19:10–27.

Accordingly, the ’512 patent teaches contacting a cell with a “therapeutically effective amount” of a DNA damaging agent and tyrosine kinase inhibitor. *Id.* at 4:16–19.

C. *Challenged Claims*

The challenged claims, claims 1–3, 5, and 6, are in independent format. Claim 1 is illustrative (paragraphing and footnote added):

1. A method of improving chemotherapeutic intervention in a patient, the method comprising:
 - (a) administering a chemotherapeutic³ DNA damaging agent to the patient;

² Example 1 of the Specification discloses that the DNA damaging agent mitomycin C activates (via autophosphorylation) the tyrosine kinase p56/p53^{lyn} which, in turn, associates with and phosphorylates the tyrosine 15 residue (Tyr 15) of the p34^{cd2} polypeptide chain. *See generally, id.* at 9:4–14:5. The cellular protein p34^{cd2} is a serine/threonine protein kinase that controls entry of cells into mitosis. *Id.* at 1:45–55 (citations omitted), 13:21–22 (citations omitted). Phosphorylation of p34^{cd2} at Tyr 15 inhibits the entry of cells into mitosis and, thus, promotes G₂ arrest. *Id.* at 13:27–32.

³ *See* Ex. 1001, Certificate of Correction dated November 23, 2010 (adding the modifier “chemotherapeutic” to all claims).

(b) administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient,

wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein, and

wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death, thereby improving chemotherapeutic intervention.

The remaining claims are similarly directed to “administering a chemotherapeutic DNA damaging agent” and “a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor” but require, for example, that the tyrosine kinase inhibitor “intracellularly inhibit[] phosphorylation of downstream effector molecules” (claims 2 and 5); “inhibit the activity of EGFR” (claim 3); “alter substrate function by inhibiting substrate phosphorylation” (claim 6); or act in combination with the DNA damaging agent “to enhance apoptosis” (claim 5).

D. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 6):

Ground	References	Basis
I	Honma, ⁴ in view of the knowledge of POSA	§ 103

⁴ Yoshio Honma et al., *Induction of Erythroid Differentiation of K562 Human Leukemic Cells by Herbimycin A, an Inhibitor of Tyrosine Kinase Activity*, 49 *CANCER RESEARCH* 331–334 (1989). Ex. 1003.

Ground	References	Basis
II	Honma, in view of the knowledge of a POSA, Honma 1992, ⁵ and McGahon ⁶	§ 103
III	Akinaga, ⁷ in view of the knowledge of a POSA	§ 103
IV	Akinaga, in view of the knowledge of a POSA, Seynaeve, ⁸ Friedman, ⁹ and Tam ¹⁰	§ 103

With respect to Ground I, Petitioner describes the knowledge of a person of ordinary skill in the art by citation to the testimony of Dr. Eastman¹¹ and to various prior art references including Honma 1992 and McGahon. *See* Pet. 24, 38 (citing Honma 1992 and McGahon, respectively). In setting forth Ground II, Petitioner incorporates the entirety of that

⁵ Yoshio 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 RESEARCH* 4017–4020 (1992). Ex. 1022.

⁶ Anne McGahon et al., *BCR-ABL Maintains Resistance of Chronic Myelogenous Leukemia Cells to Apoptotic Cell Death*, 83 *BLOOD* 1179–1187 (1994). Ex. 1029.

⁷ Shiro Akinaga et al., *Enhancement of Antitumor Activity of Mitomycin C In Vitro and In Vivo by UNC-01, a Selective Inhibitor of Protein Kinase C*, 32 *CANCER CHEMOTHERAPY AND PHARMACOLOGY* 183–189 (1993). Ex. 1004.

⁸ Caroline M. Seynaeve et al., *Cell Cycle Arrest and Growth Inhibition by the Protein Kinase Antagonist UCN-01 in Human Breast Carcinoma Cells*, 53 *Cancer Res.* 2081–2086 (1993). Ex. 1014.

⁹ BethAnn Friedman et al., *Regulation of the Epidermal Growth Factor Receptor by Growth-Modulating Agents: Effects of Staurosporine, a Protein Kinase Inhibitor*, 50 *CANCER RESEARCH* 533–538 (1990). Ex. 1031.

¹⁰ Sun W. Tam and Robert Schlegel, *Staurosporine Overrides Checkpoints for Mitotic Onset in BHK Cells*, 3 *CELL GROWTH & DIFFERENTIATION* 811–817 (1992). Ex. 1012.

¹¹ Declaration of Alan Eastman, Ph.D., in Support of Petitioners. Ex. 1002.

discussion, with emphasis on the teachings of Honma 1992 and McGahon. Pet. 41–43. Petitioner repeats this tactic with Grounds III and IV, discussing each of Seynaeve, Tam, and Freidman in Ground III (*see* Pet. 52, 53, 55–57, 59, and 60), and incorporating the entirety of that discussion into Ground IV (*id.* at 61–64).

Petitioner fails to articulate any meaningful difference in substance between Grounds I and II, or between Grounds III and IV. Given the complexity of the subject matter, however, we appreciate Petitioner’s indecision regarding whether Honma 1992 and McGahon (Grounds I/II), or Seynaeve, Tam, and Freidman (Grounds III/IV) should be designated as secondary references, or merely considered as part of the general knowledge of one ordinary skill in the relevant art. However, in order to avoid the inefficiency of addressing multiple expositions of the same challenge, we focus herein on Grounds II and IV. We do not exercise our discretion under 37 C.F.R. § 42.108(a) to decline institution of all asserted grounds as Patent Owner urges. *See* Prelim. Resp. 4.

II. ANALYSIS

A. *Person of Ordinary Skill in the Art.*

For the purpose of this Decision, we accept Petitioner’s undisputed contention that a person of ordinary skill in the art as of the effective filing date of the ’512 patent, “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.” Pet. 17 (citing Ex. 1002 ¶ 19); *see* Prelim. Resp. 5. The level of ordinary skill in the art is further demonstrated by the prior art asserted in the Petition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

With respect to the critical date, Petitioner argues that the challenged claims are entitled to an effective filing date no earlier than September 19, 1994. Pet. 16–17. Patent Owner does not expressly reject this contention, nor argue that any cited reference fails to qualify as prior art under 35 U.S.C. § 102(b). *See* Pet. 2–3 (asserting that Akinaga is prior art under § 102(b) based on “the earliest priority date to which the claims are actually entitled”); Prelim. Resp. 5 (stating that “the priority application date for the ’512 patent” is “1994”). Accordingly, we need not further address the effective date of the challenged patent at this time.

B. Claim Construction

Petitioner asserts, and Patent Owner does not contest, that the ’512 patent expired as of April 8, 2015. Pet. 17; Prelim. Resp. 8–9. Although we accord claims of an unexpired patent their broadest reasonable interpretation in light of the specification, our review of claims of an expired patent is similar to that of a district court. *See In re Rambus, Inc.*, 694 F.3d 42, 46 (Fed. Cir. 2013). Specifically, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–17 (Fed. Cir. 2005) (en banc).

i. Non-limiting Elements

The parties agree that the preamble of each challenged claim, as well as the “thereby” clause of claims 1–3 (“thereby improving chemotherapeutic intervention”), are non-limiting. Pet. 17–18, 21–22; Prelim. Resp. 5, 8. On the present record, we adopt the parties’ proposed interpretation of these claim elements. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (instructing that only those terms that are in

controversy need be construed, and only to the extent necessary to resolve the controversy).

ii. Low Molecular Weight

According to Patent Owner, the parties have previously agreed to a construction of “low molecular weight” as “having a molecular weight of less than 900 g/mol.” Prelim. Resp. 8 (citing Ex. 2001¹² at 7). We are not bound by the parties’ consensus as to the meaning of any claim term nor, in considering the meaning and patentability of the challenged claims in an *inter partes* review. Nevertheless, as this term appears to be uncontested, and absent evidence or argument to the contrary, we adopt Patent Owner’s proposed construction of this term for the purpose of this Decision.

iii. Patient

Petitioner contends that the term “patient” should be construed to encompass both animal and human subjects. Pet. 19 (citing Ex. 1001 4:20–21, 5:50–54, 5:54–55, 64–67; Ex. 1002 ¶¶ 76–77). Patent Owner agrees that the term applies to both humans and to animals in a veterinary setting, but would exclude laboratory animals treated “for medical testing purposes.” Prelim. Resp. 5; *see also id.* at 18–19.

Although intended to “benefit cancer patients” the Specification broadly encompasses “the killing of cancer cells within an animal or human subject that has a tumor.” Ex. 1001, 4:19–21; *see also* 2:65–67. Petitioner does not persuade us that anything in the Specification or prosecution history requires that the tumor arise outside of a research setting. Accordingly, on the present record, we agree with Petitioner that the term “patient”

¹² *Arch Development Corp., et al. v. Genentech, Inc., et al.*, No. 15-cv-6597, Defendants’ Joint Opening Claim Construction Brief (N.D. Ill. Aug. 2, 2016).

encompasses both animal and human subjects, and does not exclude laboratory animal testing.

iv. Administering a Therapeutically Effective Amount of a Low Molecular Weight Tyrosine Kinase Inhibitor

Petitioner proposes that the term “therapeutically effective amount” as used in the claim phrase, “administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor” be accorded its plain and ordinary meaning of “an amount that would be sufficient to have a desired therapeutic effect.” Pet. 19–21 (citing, e.g., Ex. 1002 ¶¶ 79–80). Patent Owner admits that Petitioners’ proposed definition “may be correct” (Prelim. Resp. 7) with respect to the plain and ordinary meaning, but argues that the inventors of ’512 patent expressly set forth a special definition of that term that “trumps” the common meaning. Prelim. Resp. 7–8 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005)).

In particular, Patent Owner points to column 4, lines 16 to 19 of the Specification, which defines a “therapeutically effective amount” as “an amount of a DNA damaging agent and tyrosine kinase inhibitor that, when administered to an animal in combination, is effective to kill cells within the animal.” *Id.* at 7. Patent Owner does not, however, address the argument set forth at page 20 of the Petition that this definition, though express, refers to “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.’” *See* Pet. 20.

Where the Specification reveals a special definition for a claim term, the inventors’ lexicography governs. *Phillips* 415 F.3d at 1316. Any such special definition must, nevertheless, be set forth in the specification with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d

1475, 1480 (Fed. Cir. 1994). On the present record, we are not convinced that the inventors' express definition of "therapeutically effective amount" applies to only the tyrosine kinase inhibitor as set forth in the challenged claims. Thus, while Patent Owner is free to present additional argument and evidence on this matter in the Patent Owner Response, on the current record, we are persuaded that the claim term "therapeutically effective amount" should be accorded its common and ordinary meaning. And, absent evidence or argument to the contrary regarding the common and ordinary meaning of this term, we adopt Petitioner's definition as, "an amount that would be sufficient to have a desired therapeutic effect."

v. Apoptosis

The '512 patent expressly provides that "[t]he terms, "killing", "programmed cell death" and "apoptosis" are used interchangeably to describe "a series of intracellular events that lead to target cell death." Ex. 1001 5:35–38. In accord with *Phillips*, we agree with the parties proposed construction of "apoptosis," as used in claim 6, to mean "a series of intracellular events that lead to target cell death." *See* Pet. 21; Prelim. Resp. 8.

C. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art;

(3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A decision on the ground of obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis “should be made explicit” and it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR*, 550 U.S. at 418.

D. Analysis

As discussed in above in section I(D), we address Petitioner’s challenge to claims 1–3, 5, and 6 of the ’512 patent on two distinct grounds, designated Grounds II and IV. For each of these Grounds, we begin with an overview of the asserted prior art.

i. Overview of References Asserted in Ground II

1. Honma (Ex. 1003)

Honma teaches that herbimycin A, “a selective inhibitor of intracellular tyrosine kinase,” induces erythroid differentiation of K562 human leukemic cells in a dose-dependent manner, as measured by benzidine staining. Ex. 1003 Abstract; 331–332. Herbimycin A was also found “to inhibit the growth of K562 cells at concentrations higher than 6×10^{-8} M, [with] 50% inhibition of growth occurring at 9.5×10^{-8} M” and 65% inhibition of growth at 1×10^{-7} M. *Id.* at 332, Fig. 1. In investigating the mechanism for these effects, Honma determined that “[w]hen K562 cells were labeled with $^{32}\text{P}_i$ in the presence of 5×10^{-8} M herbimycin A, the level of all tyrosine-phosphorylated proteins was greatly reduced,” including a reduction of approximately 55% of the tyrosine kinase p210^{c-abl}. *Id.* at 333.

Honma also examined the effect of herbimycin A in combination with other inducers of erythroid differentiation in K562 cells, including the DNA damaging agent Adriamycin. *Id.* at 333. Honma concludes that the combination of herbimycin A and Adriamycin “have additive or more than additive effects on [erythroid differentiation].” *Id.* at 333, Fig. 4. Honma similarly determined that “a low concentration of herbimycin A increases inhibition of cell growth of K562 cells by Adriamycin.” *Id.*, Fig. 5.

In light of these results, Honma suggests that “tyrosine kinase activity may be critically involved in growth control mechanism of K562 cells, possibly as a result of induction of terminal differentiation.” *Id.* “Herbimycin A and its derivatives might be useful as cancer chemotherapeutic agents against some types of leukemia oncogenesis where tyrosine kinase activities are implicated.” *Id.* And, “[s]ince 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.” *Id.*

2. *Honma 1992 (Ex. 1022)*

Honma 1992 notes that:

Chronic myelogenous leukemia and some cases of acute lymphocytic leukemia are characterized by the Philadelphia t(9;22)(q32;q11) chromosome translocation, in which the 5' sequences of the *bcr* gene become fused with the *c-abl* protooncogene. The resulting genes encode proteins with high activity as protein tyrosine kinases . . . [and t]he transforming activity of the chimeric gene is closely associated with its tyrosine kinase activity. Therefore, a selective inhibitor of

tyrosine kinase activity might be useful in chemotherapy of some leukemias with the Philadelphia chromosome.

Ex. 1022, 4017. Honma 1992 also notes that herbimycin A “inhibits the activities of protein tyrosine kinases encoded by several oncogenes including *v-src*, *v-abl*, and *bcr-abl*.” *Id.*

With this background, Honma 1992 focuses on experiments using the viral homolog of *c-abl*. In particular, Honma 1992 explains that the mouse C1 cell line comprises “megakaryoblastic cells established by coinfection with Abelson murine leukemia virus and recombinant SV40” which express high levels of *v-abl*. *Id.* (note omitted); *id.* at Abstract. “These cells are induced to differentiate into megakaryocytes by treatment with some inhibitors of tyrosine kinase, including herbimycin A, and inhibition of their *v-abl* tyrosine kinase activity is preceded by induction of their differentiation.” *Id.* at 4017 (note omitted).

Honma 1992 teaches that, whereas nude mice inoculated with 10^6 C1 cells died of leukemia within 30 days, “[a]dministration of herbimycin A significantly enhanced the survival of mice inoculated with C1 cells.” *Id.* Abstract, *see id.* at 4019. Honma, thus, concludes that, the “differentiation-inducing and growth-inhibitory effects [of herbimycin A] are compatible with its effects in prolonging survival of mice inoculated with leukemia cells.” *Id.* at 4019. Moreover, “[t]he present results suggest that herbimycin A and related compounds may be very effective for eliminating malignant cells from the bone marrow of patients with leukemias in which tyrosine kinase activity is implicated as a determinant of the oncogenic state.” *Id.* at 4020.

3. *McGahon (Ex. 1029)*

McGahon teaches that K562 is a chronic myelogenous leukemia cell line (CML) expressing the Bcr-Abl fusion protein. Ex. 1029, Abstract. McGahon further teaches that K562 cells are “particularly resistant to cell death via apoptosis” (*id.* at 1185) and suggests that *bcr-abl* “acts as an anti-apoptosis gene in CML cells” and that its “effect is dependent on the *abl* kinase activity.” *Id.* at Abstract. McGahon demonstrated the use of anti-sense oligonucleotides to down-regulate Bcr-Abl protein expression and, thus, reduce Bcr-Abl tyrosine kinase activity, which rendered the treated cells susceptible to induction of apoptosis by chemotherapeutic agents. *Id.* at Abstract, 1180–1184, Figs. 1–5.

McGahon suggests that in chronic myelogenous leukemia, “the elevat[ed] expression of ABL tyrosine kinase activity may act to suppress apoptosis,” “[b]y re-opening the apoptotic pathway, cells can be rendered susceptible to induction of apoptosis through DNA damage.” *Id.* at 1185. Accordingly, “[i]nhibition of *bcr-abl* to render CML cells susceptible to apoptosis can be combined with therapeutic drugs and/or treatment capable of inducing apoptosis to provide an effective strategy for elimination of these cells.” *Id.* Abstract.

ii. *Obviousness over Honma, in view of the knowledge of a POSA, Honma 1992, and McGahon (Ground II)*

Petitioner asserts that claims 1–3, 5, and 6 would have been obvious over the combination of Honma, in view of the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon. *See* Pet. 2, 22–41. Petitioner addresses the individual limitations of the challenged claims at length, including in a detailed claim chart. *Id.*

Petitioner argues that the primary reference, 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.” Pet. 2; *see id.* at 23 (citing e.g., Ex. 1003 Abstract) (“Noncytotoxic concentrations of herbimycin enhanced the antiproliferative effect of Adriamycin . . . on K562 cells. 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”).

With respect to the requirement that the DNA damaging agent and the tyrosine kinase inhibitor act in combination to enhance cell death (claims 1–3) or apoptosis (claim 6), Petitioner equates the differentiation of K562 cells in Honma with (eventual) cell death. Pet. 30 (citing Ex. 1002 ¶¶ 124–129). In particular, Petitioner argues (1) that Honma’s “Adriamycin/herbimycin A combination causes immortal cells to become mortal, thereby enhancing cell death.” *Id.* at 30 (citing e.g., Ex. 1002 ¶¶ 124–129). In the alternative, Petitioner argues that because Adriamycin and herbimycin A, individually, were known to cause cell death, one of ordinary skill in the art would have understood that Honma’s combination would as well. *Id.* at 31 (citing Ex. 1002 ¶¶ 131–134; Ex. 1034;¹³ Ex. 1026¹⁴).

Recognizing that Honma characterizes the therapeutic outcome in terms of enhanced antiproliferative effects and cell differentiation, as

¹³ Andrzej Skladanowski and Jerzy Konopa, *Adriamycin and Daunomycin Induce Programmed Cell Death (Apoptosis) in Tumour Cells*, 46 *BIOCHEMICAL PHARMACOLOGY* 375–382 (1993).

¹⁴ Declaration Under 37 C.F.R. § 1.132 of Ralph R. Weichselbaum.

opposed to apoptosis *per se*, Petitioner further argues that Mahon teaches that a reduction in Bcr-Abl tyrosine kinase activity renders cells susceptible to induction of DNA damage-induced apoptosis, whereas Honma 1992 teaches that such a reduction may be achieved with the tyrosine kinase inhibitor herbimycin A. *See e.g.*, Ex. 1002 ¶¶ 182–183. Thus, as further discussed below, “a person of ordinary skill in the art would have understood Honma to disclose a method to enhance apoptosis (and cell death).” *Id.* ¶ 182.

Petitioner relies on Honma 1992 and the testimony of Dr. Eastman as evidence that POSA would have had a reasonable expectation of success in administering the claimed combination to patients in light of that reference’s disclosure of how to dose herbimycin A in tumor-bearing mice—the use of Adriamycin in human cancer treatment being in common practice. Pet. 24–25, 42 (*citing e.g.*, Ex. 1022, 4020, Tab. 2, Fig. 4; Ex. 1002 ¶¶ 111–112, 114, 175–178); *see also* Prelim. Resp. 14 (acknowledging that the use of Adriamycin in the treatment of human cancer was known).

Petitioner further cites Honma 1992 as disclosing that treatment of K562 cells with herbimycin A inhibits p210^{c-abl} —a tyrosine kinase also known as Bcr-Abl, known to suppresses the intracellular events that lead to target cell death. Pet. 36 (*citing e.g.*, Ex. 1002 ¶¶ 122–123, 158). Pointing to McGahon as teaching that inhibition of Bcr-Abl tyrosine kinase renders K562 cells susceptible to apoptosis caused by DNA damaging agents, Petitioner argues that one of ordinary skill in the art “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.” Pet. 43 (*citing* Ex. 1002 ¶¶ 182–183). Further, according to Petitioner’s expert,

[o]ne skilled in the art would have been motivated to combine Honma with Honma 1992 because both involve cancer-related research on herbimycin A. One skilled in the art would have been motivated to further combine Honma with McGahon because both involve cancer-related research on combinations of tyrosine kinase inhibitors and DNA damaging agents in K562 cells and both consider effects on Bcr-Abl.

Ex. 1002 ¶ 173; *see also* Pet. 41 (stating that it would have been obvious to combine the three references “because they involve administration of the same tyrosine kinase inhibitor (i.e., herbimycin A) or inhibition of the same tyrosine kinase (Bcr-Abl)”).

Patent Owner argues that Petitioner has not presented sufficient data or objective evidence to show a reasonable likelihood that it would prevail in showing the unpatentability of any challenged claim. Prelim Resp. 9–25. With respect to Ground II, Patent Owner challenges, Dr. Eastman’s reasons to combine the cited references as conclusory. Prelim. Resp. 13–15, 16–17. Considering Dr. Eastman’s declaration as a whole, we find his testimony sufficient for the purpose of institution. Patent Owner will have the opportunity to cross-examine Petitioner’s expert and present its own evidence at trial.

Patent Owner further contends that under its proposed construction of “therapeutically effective amount,” each of the challenged claims requires both a “cytotoxic” amount of the low molecular weight tyrosine kinase inhibitor and “cell killing,” whereas, “Honma’s dosage of the Adriamycin/herbimycin A combination is expressly non-toxic” (Prelim. Resp. 10), resulting in cell differentiation rather than cell death or apoptosis. Prelim. Resp. 9–13; *see id.* at 6–7. As noted above in section II(B)(v), we construe the recitation of “therapeutically effective amount” in the challenged claims to mean “an amount that would be sufficient to have a

desired therapeutic effect.” This construction does not require either cytotoxicity or cell killing. Accordingly, and on the present record, we are persuaded that Honma teaches a “therapeutically effective amount” of the tyrosine kinase inhibitor.

With respect to the claim language, “wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death” (claims 1–3) and, “wherein the agent and the inhibitor act in combination to enhance apoptosis” (claim 5), we agree with Petitioner that “[t]he claims and specification provide no limits on when cell death must occur.”¹⁵ *See* Pet. 31. In light of our construction, and on the present record, we are persuaded that the differentiation of K562 cells taught by Honma correspond to the “enhance[ment] of cell death” recited in claims 1–3, and the requirement for “apoptosis” in claim 5. *See* section II(B)(iv) (defining “apoptosis” as, “a series of intracellular events that lead to target cell death”). We are likewise persuaded, on the present record, by Petitioner’s argument that in light of the teachings of Honma 1992 and McGahon, one of ordinary skill in the art would have understood that the combination of a chemotherapeutic DNA damaging agent and a tyrosine kinase inhibitor taught in Honma would enhance apoptotic cell death. *See* Pet. 43 (citing Ex. 1002 ¶¶ 182–183).

Patent Owner further argues that “Petitioners provide no explanation as to why one skilled in the art would have replaced [the antisense oligonucleotides of McGahon] with Honma’s low molecular weight

¹⁵ Accordingly, we are not persuaded by Patent Owner’s assertion that Honma or McGahon teach away from the claimed invention. *See* Pet. 11–12, 16.

inhibitor,” herbimycin A. Prelim. Resp. 16. We do not find this argument persuasive. As we understand Petitioner’s argument, McGahon is cited for the teaching that the reductions in Bcr-Abl tyrosine kinase activity increase a cell’s susceptibility to apoptosis caused by chemotherapeutic DNA damaging agents. *See* Pet. 42–43; *see also* Ex. 1029, Abstract (“Inhibition of *bcr-abl* to render CML cells susceptible to apoptosis can be combined with therapeutic drugs and/or treatment capable of inducing apoptosis to provide an effective strategy for elimination of these cells.”). Patent Owner does not persuade us that McGahon’s underlying methodology (employing antisense oligonucleotides rather than the claimed “low molecular weight” tyrosine kinase inhibitor) undermines this teaching.

Upon review of Petitioner’s analysis and supporting evidence, we determine that there is a reasonable likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–3, 5, and 6 over the combination of Honma, the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon.

ii. Overview of References Asserted in Ground IV

1. Akinaga

Akinaga examines the effect of UCN-01 (7-hydroxy-staurosporine) alone, and in combination with the DNA damaging agent mitomycin C (“MMC”). *See* Ex. 1004, Abstract; *see also* Fig. 1 (showing chemical structures of UCN-1 and staurosporine). Noting that MMC caused delays in the S and G₂M phases of the cell cycle, whereas UCN-01 blocked the cell cycle progression at G₁, Akinaga concludes that “[t]hese findings [provide] a strong indication for combining both drugs.” *Id.* at 188.

Akinaga reports that in *in vitro* studies using A431 human epidermoid carcinoma cells, “UCN-01 potentiated the antiproliferative activity of

mitomycin C.” *Id.* at Abstract; *see also, id.* (“Isobologram analysis revealed that the interaction of UCN-01 with MMC was synergistic in its antiproliferative activity.”). In vivo studies using xenografted A432 cells in nude mice similarly showed that “the combination of both drugs in a single i.v. injection exhibited greater antitumor activity than MMC and UCN-01 alone ($P < 0.01$).” *Id.*; *see id.* at 187. Akinaga reports that “[t]his synergistic antitumor effect was also confirmed in two other solid tumor cell lines, i.e. human xenografted colon carcinoma Co-3 and murine sarcoma 180,” as well as in a “P388 leukemia model, in which we saw an increased lifespan of mice when UCN-01 was combined with MMC.” *Id.* Abstract; *see id.* at 187–188. According to Akinaga, “[t]hese results suggest the feasibility of using UCN-01 in clinical oncology, especially with alkylating agents such as MMC. In addition, this combination therapy might be a novel chemotherapeutic approach to MMC-insensitive tumors in clinical trials.” *Id.* at 183.

Akinaga describes UCN-1 as “a potent and selective inhibitor of protein kinase C (PKC)” and “suggest[s] that the selective inhibition of PKC by UCN-01 might contribute to the enhancement of the antiproliferative activity of MMC.” *Id.* at Abstract, 183. Akinaga also presents, in Table 1, evidence that UCN-01 inhibits other kinases, including the tyrosine kinase pp60^{v-src} and “suggests that UCN-01 exhibits its antitumor activity by the inhibition of PKC *and/or other protein kinases.*” *Id.* at 183, 184 (italics added).

2. Seynaeve

Seynaeve states that UCN-1 “has the demonstrated capacity to inhibit a number of kinases at nanomolar concentrations including PKC ($IC_{50} = 4.1$ nm), PKA ($IC_{50} = 42$ nm), and p60^{v-src} protein tyrosine kinase ($IC_{50} = 45$

nm). Ex. 1014, 2081 (notes omitted); *see also id.* at Abstract (“UCN-01 . . . [has] “the capacity to inhibit a number of tyrosine and serine/threonine kinases.”). Seynaeve demonstrates that UCN-01 reduces tyrosine phosphorylation of four cellular proteins of *Mr* 33,000, 57,000, 83,000, and 175,000 in MDA-MB468 breast carcinoma cells. *Id.* at 2084–85, Fig. 7. Noting that “UNC-01 . . . decreased tyrosine phosphorylation of at least 4 proteins as arrest in G₁ becomes apparent” (*id.* at 2085), Seynaeve proposes a link between UCN-01’s inhibitory effects on tyrosine kinases and its inhibitory effects on the cell cycle. In particular:

The development of G₁ to S block correlates with the persistent inhibition of total phosphate labeling and tyrosine phosphorylation of discrete cellular phosphoproteins. . . .

Most notable is the decrease of phosphorylation in the *Mr* 33,500 protein species, and the inhibition of tyrosine phosphorylation in the approximately *Mr* 83,000 protein at a time when the transition from G₁ to S is occurring in these cells.”

Id. at 2085.

3. *Tam*

Tam teaches that “[s]taurosporine is a potent general protein kinase inhibitor that can suppress *in vitro* the activity of phospholipid Ca²⁺-dependent and cyclic nucleotide-dependent serine/threonine protein kinases as well as the tyrosine kinases p60^{v-src} and epidermal growth factor receptor.” Ex. 1012, 811; *see also id.* at 816 (“*in vitro* IC₅₀ levels for staurosporine are in the range of 3–8 nm for cyclic nucleotide- and Ca²⁺-dependent serine/threonine kinases and for certain tyrosine kinases”).

Tam further teaches that “DNA damage prolongs the G₂ phase of the cell cycle. This delay allows additional time for repair of DNA before mitotic onset and increases cell survival.” *Id.* at 815 (notes omitted). Tam

demonstrates that staurosporine “can uncouple mitosis from the completion of DNA replication and override DNA damage-induced G₂ delay.” *Id.* Abstract, *see id.* at 815. Thus, in suppressing G₂ delay in cells that have suffered DNA damage, “staurosporine bypasses normal checkpoints for mitotic onset” and “induces premature mitosis in cells that contain incompletely replicated genomes.” *Id.* at 811.

4. *Friedman*

Friedman discloses that “[s]taurosporine is a potent microbial inhibitor of a number of protein kinases, including protein kinase C, cyclic AMP-dependent kinase, and the tyrosine kinase pp60^{src}. Ex. 1031, Abstract. The IC₅₀ for the inhibition of these kinases by staurosporine “are within the same order of magnitude, ranging from 3 to 30 nm.” *Id.* at 533.

Friedman further discloses that “[S]taurosporine is an effective inhibitor of the EGF-stimulated receptor tyrosine kinase *in vitro*.” *Id.* Abstract. Friedman suggests that staurosporine inhibits EGFR tyrosine kinase activity by “interacting with the ATP-binding domains of the EGF receptor.” *Id.* at 538.

iii. *Obviousness over Akinaga, in view of the knowledge of a POSA, Seynaeve, Friedman, and Tam (Ground IV)*

Petitioner asserts that claims 1–3, 5, and 6 would have been obvious over the combination of Akinaga, in view of the knowledge of a person of ordinary skill in the art, Seynaeve, Friedman, and Tam. *See* Pet. 2–3, 42–67. Petitioner addresses the individual limitations of the challenged claims at length, including in a detailed claim chart. *Id.*

As an initial matter, Petitioner notes that Akinaga was distinguished during prosecution on the basis that the Examiner did not establish that

Akinaga taught a tyrosine kinase inhibitor. Pet. 14, 46; *see* Ex. 1017,¹⁶ 6 (“On this record, the examiner failed to provide the factual evidence necessary to establish a nexus between protein tyrosine kinase inhibitors and the teachings of . . . Akinaga.”). On the present record, however, we credit Dr. Eastman’s testimony that “Akinaga explicitly discloses that UCN-01 inhibits ‘pp60^{v-src},’ which is identified as ‘v-src tyrosine kinase’ in Table 1.” Ex. 1002 ¶ 96.

Briefly, Petitioner argues that the primary reference,

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.

Pet. 3. Petitioner further argues that Akinaga teaches that MMC and UCN-01 result in cell cycle arrest in different phases of the cell cycle, thus providing “a strong indication for combining both drugs.” *Id.* at 46–47 (quoting Ex. 1004, 188). According to Dr. Eastman, one of ordinary skill in the art would have understood from Akinaga that UCN-01 would enhance the cell death (apoptosis) resulting from the chemotherapeutic DNA damaging effects of MMC. *See* Pet. 58–59 (citing, e.g., Ex. 1002 ¶ 229).

With respect to the limitation of claims 1 and 2, “wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein,” Petitioner relies, in part, on Seynaeve’s teaching that UCN-01 “decreased tyrosine phosphorylation of at least 4 proteins.” Pet. 52 (citing Ex. 1014, 2085).

¹⁶ Decision on Appeal from Appln. No. 08/309,315, dated Sept. 19, 2001.

With respect to the requirement of claim 3, “wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase,” Petitioner points to the knowledge of one of ordinary skill in the art and to the teachings of Tam and Freidman. Pet. 56 (citing e.g., Ex. 1035¹⁷, 4889–90, Fig. 2); Ex. 1002 ¶¶223–25. In discussing Tam, Petitioner relies on Dr. Eastman’s testimony regarding the similarity of staurosporine and its 7-hydroxy derivative, UCN-01, and Tam’s disclosure that staurosporine “can suppress in vitro the activity of . . . tyrosine kinases p60^{src} and epidermal growth factor receptor.” Pet. 56 (citing Tam 811; Ex. 1002 ¶ 224). Petitioner similarly relies on Friedman as disclosing that staurosporine, “a close structural analog of UCN-01,” inhibits tyrosine kinases by competing with ATP at a kinase’s ATP binding domain. Pet. 56 (citing Ex. 1031, 537–538, Fig. 8; Ex. 1002 ¶ 224). “Based on this mechanism of action,” Petitioner concludes that “a POSA would have logically predicted that UCN-01 would also inhibit the tyrosine kinase activity of EGFR.” *Id.* at 57 (citing Ex. 1002 ¶ 225).

In response, Patent Owner contends that Akinaga is directed to the inhibition of protein kinase C, and to the extent it mentions pp60^{v-src}, that tyrosine kinase “is expressed only in chicken cells infected with Rous sarcoma virus,” and, thus, irrelevant to the challenged claims. Prelim. Resp. 17–18; *see also id.* at 23 (“[I]n the context of Akinaga’s teachings, UCN-01 is not acting as a tyrosine kinase inhibitor.”).

¹⁷ Shiro Akinaga et al., *Antitumor Activity of UCN-01, a Selective Inhibitor of Protein Kinase C, in Murine and Human Tumor Models*, 51 *CANCER RES.* 4888–4892 (1991).

Patent Owner does not, however, point to evidence of record that one of ordinary skill in the art would fail to equate the inhibition of pp60^{v-src} with the behavior of its cellular homolog or other tyrosine kinases. Patent Owner also fails to address Akinaga's conclusion that "UCN-01 exhibits its antitumor activity by the inhibition of PKC *and/or other protein kinases.*" Ex. 1004, 183 (italics added). Accordingly, at this stage in the proceeding, we credit Dr. Eastman's testimony regarding Akinaga, and how that reference would be understood by one of ordinary skill in the art.

With respect to the requirement of claim 1 that the low molecular weight tyrosine kinase inhibitor "inhibit the activity of more than one tyrosine kinase protein," Patent Owner further argues that Seynaeve provides no conclusion regarding the mechanism by which UCN-01 leads to "decreased phosphorylation." Prelim. Resp. 20. Patent Owner also challenges the relevance of Akinaga and Tam to the inhibition of EGFR (claim 3) because Akinaga focuses on the effect of protein kinase C; and although Tam admittedly reports that staurosporine inhibits the activity of pp60^{v-src}, the cell line Tam worked with allegedly contained neither p60^{v-src} nor epidermal growth factor receptor; and because staurosporine "inhibits a wide range spectrum of tyrosine kinases." Prelim. Resp. 21; *see also* 20–23. We do not find Patent Owner's arguments persuasive on the present record and, as above, at this stage in the proceeding, we credit Dr. Eastman's testimony regarding the prior art references, and how they would be understood by one of ordinary skill in the art.

Upon review of Petitioner's analysis and supporting evidence, we determine that there is a reasonable likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–3, 5, and 6 over the

combination of Akinaga, the knowledge of a person of ordinary skill in the art, Seynaeve, Tam, and Friedman.

III. CONCLUSION

For the foregoing reasons, we find that the information presented in the Petition establishes a reasonable likelihood that the Petitioner would prevail in showing that claims 1–3, 5, and 6 of the '512 patent are invalid as obvious over the prior art.

This is not a final decision as to the construction of any claim term or the patentability of claims 1–3, 5, and 6. Our final decision will be based on the full record developed during trial.

IV. ORDER

For the reasons given, it is

ORDERED that *inter partes* review is instituted with regard to the following asserted grounds:

Claims 1–3, 5, and 6 of the '512 patent under 35 U.S.C. § 103(b) as obvious over the combination of Honma, the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon; and

Claims 1–3, 5, and 6 of the '512 patent under 35 U.S.C. § 103(b) as obvious over the combination of Akinaga, the knowledge of a person of ordinary skill in the art, Seynaeve, Tam, and Friedman.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '041 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial is limited to the grounds listed in the Order. No other grounds are authorized.

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