UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,[1]
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00731
Patent 7,846,441

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

[1] Pfizer, Inc. is presently the sole real-party-in-interest in these proceedings. (*See* Paper 13 at 2.)

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I. INTRODUCTION

PO's Dr. Susan Desmond-Hellman claimed to be the inventor of a method of treating human HER2+ breast cancer patients with a combination of paclitaxel and trastuzumab. But that idea was not hers. Preclinical studies of the same combination treating the same disease already had been published by Dr. Baselga and colleagues at Memorial Sloan Kettering, with "dramatic" results. That work unmistakably was done "with the intention to look at trying to predict what can be helpful in patients." (Ex. 1091(Hellmann)_48:19-49:1.) And Baselga even explicitly suggested "***[c]linical*** trials."[2] The '441 patent "invention" was already out there for the world to see. That is the epitome of obviousness.

PO says it is nevertheless entitled to a patent because Dr. Desmond-Hellmann proposed to modify PO's clinical trial to include a trastuzumab-paclitaxel arm when, according to PO, no one had yet publicly proposed or conducted a clinical trial using the combination. But even if Baselga had not previously proposed "clinical trials"—which he did—this idea could not entitle PO to a patent on the therapy. [redacted]

[2] Emphasis is added unless otherwise noted.

[redacted] PO's assertion that preclinical research has "limitations" weaves a tale that could be woven in any case.

The '441 patent claims are unpatentable.

II. CLAIM CONSTRUCTION

A. "Administering A Combination"

Petitioner agrees for this IPR that the BRI of "administering a combination" is administering drugs "as part of the same treatment regimen." (*See also* Ex. 1085¶¶83-84.)

B. "Extend The Time To Disease Progression In Said Human Patient, Without Increase In Overall Severe Adverse Events"

The Board construed this term to be relative to an ***untreated*** patient. Petitioner agrees. The Examiner gave PO a clear choice between "***untreated*** patients," "***[p]atients who received*** antibody or ***taxoid alone***," or "[p]atients who received antibody and an anthracycline." (Ex. 1011_2:324-25.) PO represented the term would be "readily understood" as "relative to an ***untreated patient***." (*Id.*_2:356.) Dr. Desmond-Hellmann testified that "[o]utside of clinical trials" it "would ***not*** be a typical use of the term 'untreated'" to say "that a patient treated with paclitaxel alone is an untreated patient." (Ex. 1091_139:14-19.) Further, PO's expert agreed "there can be ***no confusion***…that [PO] was choosing the comparator ***untreated patients rather than taxoid alone***." (Ex. 1087_225:15-226:13.) PO may

now regret its choice, but the Board should not condone PO's unjust attempt to offer one interpretation to overcome one rejection ground, and a different interpretation to overcome another.

PO asserts "Petitioner's own expert…opined that a POSA would understand that the appropriate comparison is to a patient treated with a taxoid alone" and that "the understanding…is not in dispute." (POR 4, 38.) But PO omits Dr. Lipton's acknowledgement in the same paragraph it cites that "during prosecution, Patent Owner asserted that the appropriate comparison for the term 'extend the time to disease progression' is to compare the claimed combination treatment to no treatment at all," and that he therefore "considered this alternate claim construction as well." (IPR2017-002063, Ex. 1102¶112.h.) Dr. Lipton did not attempt, nor need, to reconcile the applicants' prosecution statement with the specification because the difference "[did] not impact [his] analysis." (*Id.*)

There also is no inconsistency with a view that "adverse events" "happen[] during treatment with a drug or other therapy." (POR 37.) The "adverse events" limitation did not stop PO from stating the appropriate comparison is "relative to an ***untreated patient***." Moreover, even if PO's chosen construction "make[s] no sense" (POR 36-37), PO still should be held to its prosecution statement. *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1300-01 (Fed. Cir. 2014). (*See also* Ex. 1085¶¶85-88.)

III. ARGUMENT

The Board's correct adoption of PO's prosecution interpretation should end this IPR. PO's expert conceded she "***ha[s] not***" opined "that Baselga '96 combined with Baselga '94 does not suggest that the claimed combination would extend the time to disease progression ***as compared to untreated patients***." (Ex. 1087_274:5-18.) PO's briefing likewise argues only lack of expectation of success in extending TTP relative to a patient treated with ***a taxoid alone***." (POR 46-53.)

Even under the erroneous construction to which PO now backpedals—comparing to ***paclitaxel alone***—the claims are obvious. The claimed benefits under PO's own view are merely inherent results of a previously-suggested combination. In any event, POSAs would have expected those benefits from Baselga's express teachings. Although PO asserts Baselga's mouse models had "limitations" that "restricted their ability to predict safety and efficacy in human patients" (POR 2), unrestricted predictiveness is not the standard for non-obviousness. PO's criticisms boil down to the same demand for "absolute predictability of success" (Paper 29, 15) that was rightly rejected at institution. (*See* Ex. 1086 ¶¶78-81.)

PO's criticisms also defy logic. PO identifies no purpose for which the Baselga '94 study was conducted, sponsored, and published by ***Memorial Sloan Kettering Cancer Center, Genentech*** and the American Society of ***Clinical***

Oncology other than to predict human effects. Dr. Desmond-Hellmann confirmed:

> Q: Was the thought that [the Baselga study] might be useful research to investigate whether Herceptin could be useful in humans with Taxol?
> THE WITNESS: All the preclinical research is done with the intention to look at -- trying to predict what can be helpful in patients. That -- that's typical.

(Ex. 1091_48:19-49:1.) Contemporaneous publications expressly described Baselga '94 as "motivation for clinical evaluation" of the claimed combination and "the basis" for clinical trials. Nor does Herceptin®'s unpublished "development history" assist PO. That PO felt sufficiently confident to proceed to Phase III trials based on preclinical results alone reflects the expectation of success they provided.

Finally, "objective indicia" do assist PO; they are unsupported, bear no nexus to the claimed invention, and are not commensurate with its scope.

A. Baselga '96 And '94 Taught Administering The Claimed Combination To Humans

1. Baselga '96 taught administering the claimed combination to humans.

PO concedes Baselga '96 reported trastuzumab "markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, ***and paclitaxel***," and that "clinical trials of ***such*** combination therapy are currently in progress." (Ex. 1004 at 15.) PO also concedes "such combination

therapy" refers to the "same studies disclosed in Baselga '94," which used "rhuMAb HER2 combined with…a taxoid (paclitaxel)." (POR 30, 39-40.) The only reasonable interpretation is that trials of trastuzumab-paclitaxel (as well as cisplatin and doxorubicin) were "currently in progress." (Exs. 1007¶59; 1085¶104.) PO's expert conceded "[o]ne might interpret it that way, yes." (Ex. 1087_252:20-253:22.) And when Baselga '96 was published and read by POSAs, clinical trials of the claimed treatment ***were*** ongoing. (Exs. 1004 at 9; 2011¶29; 1087_254:03-257:02, 259:17-21;[3] *see also* Ex. 1085¶¶102, 103, 105, 106; Ex. 1086¶¶ 78, 79, 131, 157-158.)

Moreover, the idea to treat HER2+ breast cancer patients with the claimed combination is immediately apparent to readers of Baselga '94 and '96. The purpose of "preclinical work on Herceptin and Taxol combinations at Memorial Sloan Kettering" was "to understand different combinations of how one thinks about treating patients" and "to predict what can be helpful in patients." (Ex. 1091(Hellmann)_48:11-49:1.) No one contends Memorial Sloan Kettering inserted human tumors into mice to benefit the mice. (*See id.*) PO's assertion that Baselga '96 fails to even "***suggest***" treating humans with the claimed combination is frivolous. Baselga '94 taught administering the claimed combination to humans.

[3] Petitioner is not relying on "***prior*** systemic [paclitaxel] therapy." (POR 39.)

(*See* Ex. 1086¶¶158-162.)

PO's attempts to discredit Baselga '94 (co-published by ***its own researcher***) revise history. ***First***, POSAs did ***not*** wait for the study results to be published in a full, peer-reviewed paper before drawing conclusions from them. (POR 41.) PO ignores that peer-reviewed publications, which PO's expert "did not take into account," described Baselga '94 as providing "motivation for clinical evaluation" and being "the basis for a planned clinical trial." (Exs. 1072 at 8; 1073 at 11; 1088_117:6-22, 120:25-121:5; 1086¶¶156-157; *see also* Ex. 1087_239:5-17.) PO's argument is code for "ignore this piece of §102(b) prior art," but there is no "full, peer-reviewed" requirement for prior art. POSAs, including PO's researchers, ***did*** consider Baselga '94 to be predictive. (Ex. 1073 at 11; *see also* Ex. 2004 at 5; Ex. 1085¶¶107-110.)

Second, PO's general criticisms of preclinical research ignore reality and what Baselga '94 discloses. PO first criticizes Baselga '94 for being "based on a single cell line." (POR 41-42.) But its criticism is not even supported by the reference it quotes, which states only "the use of a series of tumors ***(where appropriate/available) may*** be required to determine the sensitivity of a particular neoplastic disease to either a single or a combination chemotherapy." (*Id.*) PO also conveniently omits the the very next line—"this must be considered in the context of reducing animal usage, cost, ***and the value of additional data obtained***" (Ex.

2052 at 261)—which shows that Baselga's choice to not try more cell lines could appropriately have reflected confidence in the results. PO also ignores another contemporaneous paper from the same author—Dr. Robert Clarke—stating while "it is entirely ***possible*** that no single model will adequately address all aspects of breast cancer biology," it is "***equally likely*** that, for any specific biological property, ***there will be at least one model that is adequately suited to the task***." (Exs. 1074 at 3; 1088_198:14-199:11; 1087_146:7-16.) As Dr. Clarke stated at the time, "[w]hether the use of a single model is appropriate will depend upon the nature of the question, the availability and characteristics of the model(s), and the investigator's evaluation of the scientific concerns." (*Id.*_201:22-202:05; *see also* Ex. 1085¶¶111-113; Ex. 1086¶¶59, 104.)

As Dr. Clarke now explains, according to these considerations, Baselga's cell-line choice made sense because it had high levels of HER2 and had previously responded to trastuzumab. (Exs. 1086¶¶61-63, 114; 2065 at 259.) Given the study's purpose and results, use of multiple cell-lines would not have been considered necessary. (Exs. 1086¶¶99-116; 1072 at 8; 1073 at 11.) Notably, PO's preclinical expert, Dr. Kerbel, admitted the Baselga '94 authors "in considering the nature of the question, the availability and characteristics of the models, and their evaluation of appropriate scientific concerns, decided that testing in the BT-474 cell line was appropriate" and he could not "recall any specific criticism" of the

authors for having done so. (Ex. 1088_202:17-203:15; *see also* Ex. 1085¶114; Ex. 1086¶69.)

PO's criticism of Baselga's "site of implantation"—subcutaneous—fares no better. (POR 42.) Dr. Kerbel conceded the reason in the cited literature (another Clarke paper) for disfavoring subcutaneous implantation in some circumstances—reduced "take rate" and ability to "facilitate metastatic spread"—was "***not a concern*** in the Baselga '94 study." (Ex. 1088_227:3-228:3.) He also admitted POSAs "wouldn't have considered the use of subcutaneous implantation to be a design flaw in the Baselga '94 study" and he is "not aware of anyone at the time, or even since, outside of the context of these proceedings, having criticized Baselga and colleagues for using subcutaneous implantation." (*Id.*_224:21-225:15; *see also* Ex. 1085¶¶115-117; Ex. 1086¶¶69, 70.)

That just leaves PO's general criticisms of preclinical mouse studies. (POR 7-11.) These criticisms ignore the reality that POSAs ***did*** consider Baselga '94 to be predictive. (Ex. 1073 at 11 2111 at 73 ("Paclitaxel was selected [to combine with trastuzumab] because of its activity in metastatic breast cancer ***and preclinical studies that supported its use***."); *see also* 2004 at 5.) They also are unsupported by the cited references, most of which do not reflect the state of the art in the relevant timeframe in ***1997***. (POR 7-9 (citing Exs. 2023 (Marsoni ***1984***) and 2075 (Bibby ***1999***)); Exs. 1087_126:17-128:5; 1088_134:16-23.) And PO's

primary reference—Gura '97—is a non-peer-reviewed "news" article that, under PO's own standards, should not be believed. (Exs. 2051; 1087_120:15-123:21; 1088_135:7-136:24, 137:15-138:14.) Moreover, these references relate to "drug screening," *i.e.*, "for agents that were not known to have activity for a particular cell line or any cell line," not agents known to have activity against breast cancer cells, as with Baselga '94. (Exs. 1086¶¶86-88, 105, 139; 1088_140:8-141:12.)

PO argues mice and humans are different, and some human toxicities cannot be tested in mice. (POR 9-10.) However, Dr. Kerbel himself agreed that, as of the mid-1990s, animal models were "***critical*** for the evaluation of new agents and therapeutic approaches for the treatment of breast cancer." (Exs. 1088_195:22-197:2; 1074 at 1.) PO, its experts, and others have successfully obtained patents on human therapies based solely on mouse studies. (Exs 1076; 1077.) Dr. Kerbel admitted his own patent claims human antibody-chemotherapy treatments for cancer based solely on a single ***mouse*** study using ***subcutaneous*** implantation of a ***single*** tumor type in a ***single*** cell-line. (Ex. 1088_246:10-249:23, 250:23-251:12.; *see also* Ex. 1086¶¶69, 70, 130.)

Finally, PO asserts Baselga '94's "note" that "clinical studies are underway" is "just a generic reference to clinical trials of rhuMAb HER2" (POR 31.) But PO provides no support for this interpretation, which does not make sense in the context of an abstract demonstrating superiority of combination treatment. PO

apparently is relying on its own internal investigation into whether there were ongoing studies of the combination underway at the time. (*Id.*) PO does not share details of its investigation, much less establish no trials were being planned. In any event, PO's investigation was not publicly available before the '441 patent's priority date, and does not change Baselga '94's clear statement.

At base, Baselga '94 ***did*** motivate clinical investigation, and there is no evidence POSAs ever criticized it on PO's bases or otherwise. PO never explains why Baselga's mouse studies were conducted in the first place if they were truly thought not to be predictive. Memorial Sloan Kettering is not in the business of treating mouse cancer. (Ex. 1091_48:11-49:1.) And if POSAs were not expected to read Baselga '94 as predicting clinical results, why was it published in the Proceedings of the American Society of ***Clinical*** Oncology? To believe PO is to believe (1) its own researchers and collaborators were publishing flawed, non-predictive results in journals about ***clinical*** (human) oncology, and (2) it authorized clinical trials with no reasonable expectation of success. Neither belief makes any sense. (*See also* Ex. 1088_28:17-29:4, 29:15-30:8; Ex. 1085¶118; Ex. 1086¶77-81.)

PO's arguments also forget how PO obtained the '441 patent. When faced with rejection over another Baselga reference—Baselga '97—PO successfully argued Dr. Desmond-Hellmann conceived of the entire invention with all its

limitations before December 12, 1996. (Ex. 1011_2:237-39.) Proof of conception requires more than the reasonable expectation of success required for obviousness. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986). Yet, to prove conception, all PO presented corresponding to the claim elements was a "plan" to treat humans with the trastuzumab-paclitaxel combination. (Exs. 1011_2:119-47; 1091_26:23-29:6.) PO did not present any results, much less results showing the combination would work to treat breast cancer in humans, extend TTP, or result in no increase in "severe adverse events." (*Id.*; Ex. 1091_29:7-31:4.) Thus, all "doubt" PO spins equally applied to Dr. Desmond-Hellmann's "plan" and successful conception "proof," and it would be unjust now to use that "doubt" to overcome Petitioner's obviousness challenge.[4] (*See also* Ex. 1085¶¶119-122.)

[4] According to Dr. Desmond-Hellmann, at the time of her alleged conception, she knew of ***unpublished*** UCLA data reporting preclinical results for the claimed combination that were not as good as Baselga's. (Ex. 1091_39:4–41:5, 71:18–77:5.) Yet under PO's arguments, POSAs somehow had ***more*** reason to doubt the predictability of Baselga's ***public*** preclinical work than did Dr. Desmond-Hellmann when she was credited with conceiving the entire invention.

2. By 1996, paclitaxel was an accepted HER2+ breast cancer treatment.

POs argument that POSAs would have avoided the claimed combination because of "significant concerns with using taxoids to treat HER2-positive breast cancer" (POR 16-17, 43) is absurd. The claimed combination ***already*** was being publicly tried, with trastuzumab described as "not increas[ing] the toxicity of paclitaxel." (Exs. 1005 at 4; 1004 at 15.) The safety of the combination is merely a natural result; Dr. Desmond-Hellmann did nothing to contribute to those properties. (Ex. 1091_60:23-62:20.) By 1996, ***paclitaxel was FDA-approved for the treatment of breast cancer*** and, as PO's clinical expert admitted, "one of the most promising treatments for breast cancer." (Exs. 1025; 1018 at 5; 1087_66:11-16; 69:19-70:5.) Paclitaxel was used ***both*** first and second-line; it was labeled for second-line treatment, [redacted]

To the extent the Taxol® label warned of adverse events, they were rare and reversible. (Exs. 1025 at 1 (hypersensitivity reactions in ***2%*** of patients); 2105 at 7 (hypersensitivity reactions "were severe in less than 2% of patients and 1% of the courses. No severe reactions were observed after course 3"); *id.* ("Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was

generally rapidly reversible.").) They also did not stop the FDA from approving paclitaxel for breast cancer. PO's expert acknowledged the Physicians' Desk Reference PO relies on "actually state[d] how to prevent those reactions" and "the benefit [of paclitaxel treatment] outweigh[ed] the risk." (Ex. 1087_113:22-115:6.) After all, as PO repeatedly points out, these are terminal cancer patients.

PO relies heavily on an ***in vitro*** study which concludes "breast cancers that overexpress [HER2] will not respond well to Taxol." (POR 17, 43; Ex. 2029 at 1362.) However, PO's expert admitted that study "would not have dissuaded clinicians from providing paclitaxel to metastatic breast cancer patients," and she was not aware of "any report that any physician was dissuaded from using paclitaxel in HER2-positive patients by this Yu paper." (Ex. 1087_93:17-94:21, 262:22-263:24.) PO also omits that a contemporaneous study of ***human patients*** showed "HER2 over-expression seems to confer ***sensitivity*** rather than resistance to taxanes." (Exs. 1078; 1079 ("[P]atients with HER2-positive tumors had a ***significantly higher probability*** of responding to paclitaxel than did those with HER-negative tumors."); 1087_95:24-98:25, 99:23-103:5; *see also* Ex. 1085¶¶123-127.)

PO also identifies nothing in the prior art teaching the claimed combination was thought to be unsafe. To the extent the combination had not yet been tried in humans, and paclitaxel was not yet FDA-approved for first-line therapy (POR 24-

25), that is irrelevant under the obviousness standard, which is met by ***a reasonable expectation of success*** and obviousness ***to try***. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (rejecting argument that, because a drug's properties need to be "verified through testing" it is necessarily patentable, stating "cannot be the proper standard since the expectation of success need only be reasonable, not absolute."). PO also contradicts its own prosecution argument that Dr. Desmond-Hellmann conceived of the entire invention before it was tried in humans. (Exs. 1011_2:237-39; 1091_29:8-11.)

3. Any motivation to try the trastuzumab-anthracycline combination does not establish non-obviousness.

Any motivation to try the trastuzumab-anthracycline combination (POR 14-16, 44-45) does not establish non-obviousness. "[A] finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed…is the preferred, or most desirable, combination." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Additionally, there certainly was a motivation to try the claimed combination without anthracyclines, which Baselga '94 reported achieved superior results. (Exs. 1005 at 4; 1007¶74.)

PO's expert also acknowledged "it was known as of the mid-1990's that anthracyclines had the potential for cumulative cardiotoxicity." (Ex. 1087_35:18-

25.) While PO tries to downplay this, PO's expert acknowledged that "the most commonly used method to prevent anthracycline cardiotoxicity is to ***stop the administration of these drugs*** when predetermined empiric cumulative dose has been reached." (*Id.*_37:2-15; Exs. 2062¶50; 1085¶25; 1033 at 11-12.)[5] And PO does not even address the problem of anthracycline ***resistance***, which led to approval of other chemotherapies, including paclitaxel, as second-line treatment for patients who failed anthracycline treatment. (Exs. 1085¶26; 2105 at 6; 1087_32:4-15.) While these concerns may not have led POSAs to abandon anthracyclines, even PO's expert admitted "it would have made sense to go ahead with Herceptin ***plus a different chemotherapy***, at least in patients who had been found to be either resistant to anthracyclines, or who had reached the cardiotoxic cumulative dose of anthracyclines," with paclitaxel "being one of them." (Ex.

[5] The other techniques identified by PO—altering the dose schedule or administering anthracycline with cardioprotectant dexrazoxane (Zinecard)—led to concerns about "whether antineoplastic activity is preserved," and/or had data showing "lower response rates and faster tumor progression times." (Exs. 1033 at 11; 1087_50:18–52:20, 54:9–19.) [redacted]

1087_275:9-23.) In any event, that the prior art taught "a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *see also* Ex. 1085¶130.

4. Herceptin®'s development history confirms *obviousness*.

PO's reliance on Herceptin®'s "development history"—that it first commenced human trials with ***anthracyclines*** (POR 21-26, 43-45)—is misplaced. If anything, it establishes ***obviousness***. PO's internal documents confirm that none of the purported concerns it raises here—Baselga '94 "design flaws", HER2+ "resistance" to paclitaxel, paclitaxel's toxicity—were factors in the decision to test the claimed combination in humans. (Exs. 2002-06.) They also bely PO's assertion that POSAs would have sought to manage anthracycline toxicity rather than use paclitaxel. (*Id.*) Nor has PO identified any "unique" insight Dr. Hellmann brought. (POR 24, 43-44.) Rather, [redacted] (Exs. 2004 at 5; 1011_2:119-47; 1091_26:23-31:4, 33:13-35:16, 39:4-46:16, 47:22-51:18.) That PO felt confident enough to test the claimed combination first in Phase III trials—

which PO's expert admits was "highly unusual" (Ex. 2062¶115)—reflects the expectation in the field, based on preclinical data, that the combination would be safe and effective. (Ex. 1087_212:7-213:10; *see also* Ex. 1085¶¶128-132; Ex. 1086¶¶119-123.)[6]

B. The Claimed Clinical Benefits Do Not Establish Patentability

1. The claimed benefits are inherent results of an obvious combination.

In a last-ditch effort to save its claims, PO argues POSAs would not have reasonably expected the claimed clinical benefits. (POR 5-6, 46-53.) According to PO's own positions, however, these benefits are merely inherent results of an obvious combination. PO admits that "[w]hen [trastuzumab is] administered with a chemotherapy in the 'taxoid' family, and in the absence of…'anthracyclines,' this claimed combination therapy significantly extends the time to disease progression

[6] [redacted] PO's expert admitted she was not aware of any data suggesting a "***negative*** result" combining trastuzumab-paclitaxel. (Ex. 1087_83:3–18; *see also* Ex. 1091_74:18–77:5.)

('TTP')…without increasing the side effects of chemotherapy." (POR 1-2.) Dr. Desmond-Hellmann testified that "to the extent that Taxol and Herceptin are safe and effective for women with HER2 positive metastatic breast cancer, that is a property of that combination" that was merely "discovered." (Ex. 1091_66:9-67:9.)[7] And, in successfully antedating Baselga '97, PO and Dr. Desmond-Hellmann similarly argued that the claimed benefits naturally flowed from this known combination. (POPR 35 ("[T]he detailed study design in the amended Phase III protocol—***which reflects each claim limitation***—is plainly sufficient to establish conception …"), 36 (records showing a patient had completed a "total course of therapy" evidenced reduction to practice); Ex. 1011_2:239, 310-12.)

It is well-established that inherent results of an obvious treatment cannot establish patentability. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *In re Huai-Hung Kao*, 639 F.3d 1057, 1071 (Fed. Cir. 2011). This is because "[n]ewly discovered results of known processes directed to the same purpose are not patentable." *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). Baselga disclosed treating HER2+ breast cancer

[7] She was not even the first to discover them: "Steve Shak would have known that the combination was safe and effective before [her]." (Ex. 1091_70:15–18.)

patients with the claimed combination. (Exs. 1004 at 15; 1005 at 4; PET 43-45.) And there was nothing new about the dosages used in PO's clinical trial. (Exs. 1085¶135; 1001_26:35-30:27; 2105 at 8.) Thus, "[t]he claimed process here is not directed to a new use; it is the same use" of the combination taught by Baselga. *Abbott Labs. v. Baxter Prods., Inc.*, 471 F.3d 1363, 1369 (Fed. Cir. 2006). "[R]ecognition of a new property of the prior art process" (*i.e.*, allegedly superior efficacy with comparable safety) cannot establish patentability. *Id.*; *see also* Ex. 1085¶¶133-135.

2. POSAs reasonably would have expected the claimed efficacy benefit.

Even if expectation of achieving the claimed benefits were necessary, it is established here. PO and its expert do not even contend that extended TTP compared to ***untreated*** patients under the Board's construction would have been unexpected. (POR 46-49; Ex. 1087_274:5-275:8.) Even under PO's construction, POSAs reasonably would have expected the claimed combination to extend TTP compared to ***paclitaxel alone***. Baselga '96 described TTP from trastuzumab treatment as "***unusually long***," while PO and its expert contend HER2+ patients were believed to "***not respond well***" to standalone paclitaxel. (Ex. 1004 at 9, 13; POR 17, 21, 43; Ex. 2062¶57.)

This expectation of efficacy benefit would have been bolstered by Baselga

'96 and '94's report of synergistic cytotoxicity of the claimed combination—the best of any tested—leading to "clinical trials." (Exs. 1005 at 4; 1007¶76; 1088_84:17-85:11.) And although Baselga '94 reported ***response rate*** (*i.e.*, shrinking tumors), that was a widely-used "surrogate endpoint" for TTP in preclinical and early-phase trials. (Exs. 1080 at 3-4; 1085¶49, 73, 136-142; 1086¶¶132-36, 162.)

3. POSAs reasonably would have expected the claimed safety benefit.

There also is no legitimate dispute POSAs would have expected (and did expect) trastuzumab ***not*** to increase severe adverse events compared to paclitaxel alone. Baselga '96 taught trastuzumab "was remarkably well tolerated," with an "absence of significant toxicity." (Ex. 1004 at 11; *see also* Ex. 1087_242:14-243:2.) Baselga '96 and '94 both taught no increase in toxicity of paclitaxel when administered with trastuzumab in mice. (Exs. 1005 at 15; 1005 at 4.) PO argues "[t]he increased cardiotoxicity of rhuMAb HER2 combined with ***anthracyclines*** was completely ***unexpected***." (POR 25, 58-59.) But as PO's expert acknowledged, this merely confirms that "based on the preclinical and early phase clinical data with Herceptin available before the Phase III study, none of that suggested that adding Herceptin to chemotherapy would increase the overall severe adverse events." (Ex. 1087_216:7-219:5; *see also* Exs. 1088_222:3-21; 1091_87:19-88:3.)

PO's assertion that "[t]he minimal toxicity of rhuMAb HER2 alone says nothing about potential safety issues when combined with other drugs" (POR 51) misses the point. PO's experts agree a POSA would not have expected trastuzumab to ***increase*** severe adverse events. The general need to confirm expectations through testing does not show non-obviousness. *Pfizer*, 480 F.3d at 1364; *see also* Ex. 1085¶¶143-147; Ex. 1086¶¶118-123.)

C. The Claimed Combination Would Have Been Obvious To Try

POSAs at least would have found the claimed combination obvious to try. (PET 49; Ex. 1007¶79.) Bizarrely, PO argues the claimed combination "was not even among a finite number of options that a POSA would have pursued." (POR 53.) Yet, at the time, only ***four*** trastuzumab therapies had been publicly proposed and tested: (i) standalone; (ii) with paclitaxel; (iii) with anthracycline; and (iv) with cisplatin. The paclitaxel combination was ***most effective*** in preclinical studies, and the prior art stated that clinical trials were "underway." (Exs. 1085¶148; 1005 at 4; 1004 at 13.) It cannot legitimately be suggested that trying the best known option was non-obvious.

PO's argument regarding purported "unpredictability" based on the general failure rate in clinical studies (POR 54-55) also fails. The Federal Circuit has rejected generalized arguments asserting success in one development phase does not always translate to the next. *Cf. NantKwest, Inc. v. Lee*, 686 Fed. App'x 864,

870 (Fed. Cir. 2017) ("The fact that *in vitro* success does not always translate into *in vivo* success cannot defeat summary judgment [of obviousness]."). And "obviousness cannot be avoided simply by showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364. Moreover, "likelihood of achieving FDA approval," the standard PO's expert admitted she applied (Ex. 1087_116:7-118:7; *see also* Ex. 1088_140:8-142:13, 145:11-16, 176:11-178:17), is not a prerequisite to obviousness. *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). According to PO's argument, no matter how clear the prior art teachings, a claimed treatment could never be obvious unless results of a Phase III clinical trial were disclosed. That is not the law. *In re Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1998) ("Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice."); *see also* Ex. 1085¶¶148-153; Ex. 1086¶¶148-153.

D. "Objective Indicia" Do Not Establish Non-Obviousness

Alleged "objective indicia" (POR 55-61) do not assist PO.

First, to the extent there was a "long-felt-but-unmet need" for an effective treatment for HER2+ breast cancer (POR 55-56), it was satisfied by ***trastuzumab*** alone. The reference PO cites reports the "few extra months of coherent, pain-free

life" were attributed to the antibody. (Ex. 2018 at 887.) PO's expert admitted she does not "identify any document, other than the patent, that suggests that there was a long-felt need that was met ***by the combination of Herceptin and Taxol***" (Ex. 1087_355:15-356:10). *Cf. Boehringer Ingelheim Int'l GmbH v. Abbvie Biotech. Ltd.*, IPR2016-00409, Paper 46 at 43-45 (PTAB July 6, 2017) ("[I]t appears…that the driving force behind the satisfaction of a long-felt need…was the introduction of the first fully human anti-TNFα antibody, not the claimed dosing regimen."); *see also* Ex. 1085¶¶155-157.

Second, any "praise" (POR 57) also was for ***the antibody itself***. (Exs. 2034; 2018 at 887.) The reference PO cites notes it was "swamped by demand" for trastuzumab ***as early as 1995***, before PO contends it began trials of the claimed combination. Praise with no nexus cannot support non-obviousness. *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008); *see also* Ex. 1085¶¶167-169.

Third, PO identifies no ***unexpected*** clinical benefits. (POR 57-60.) There is no showing the combination increased TTP compared to ***antibody*** alone—as described in the patent, PO's trial testing the claimed combination included no antibody-only arm, and no antibody-only TTP data is disclosed in the patent. (Ex.

1001_26:35-30:25.) And, although the study purported to show extended TTP for the combination compared to ***paclitaxel*** alone,[8] that was ***not*** unexpected. As explained above, the "unusually long" TTP for HER2+ patients on trastuzumab reported in Baselga '96 contrasted with what PO asserts were poor results for standalone paclitaxel, as well as the Baselga '94 results, would have led POSAs to expect addition of trastuzumab to extend TTP. (Section B.2, *supra*.) Nor was the ***lack*** of increased toxicity (POR 58-60) unexpected. PO and its experts assert that ***increased toxicity*** of trastuzumab in combination with anthracycline was ***unexpected***. (Section B.3, *supra*; *see also* Ex. 1085¶¶163-165.)

Fourth, PO has shown no nexus between commercial success of ***Herceptin®*** and the claimed invention. (POR 60-61.) PO omits that Herceptin® was approved from the outset "***as a single agent***" for treatment of patients "who have received one or more chemotherapy regiments for their metastatic disease." (Ex. 2012 at 1.) Although Herceptin® ***also*** was approved as first-line treatment with paclitaxel, PO has not shown how much, if any, commercial success was due to the claimed combination rather than Herceptin® itself. Notably, PO's expert testified she had "concerns" with administering paclitaxel, alone or in combination treatment, for up

[8] Dr. Tannenbaum testified the patent data did not show ***statistically significant*** increase in TTP. (Ex. 1087_196:15–197:12.)

to five years after approval of Herceptin®. (Ex. 1087_261:2-262:11.)

PO also has not shown its "objective indicia" are commensurate with the scope of the claims, which generally permit ***any*** taxoid. PO presents no evidence for trastuzumab/***docetaxel***. (Ex. 1001_11:4-15 (identifying "docetaxel (Taxotere®…)" as a taxoid).) PO's assertion that "***Petitioner*** has not offered any evidence that paclitaxel is not representative of taxoids generally" (POR 60, n.16) is unavailing, as ***PO*** bears the burden on nexus. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387 (Fed. Cir. 1998); *see also* Ex. 1085¶154.

Finally, PO takes issue with Petitioner's rebuttal to Dr. Sliwkowski's prosecution declaration. (POR 61-63; PET 59-62; Ex. 1007¶¶ 183-89.) But PO submits only "naked attorney argument" in response, which is "insufficient to establish unexpected results." *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

E. These Proceedings Are Constitutional

This IPR is constitutional. *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1288-93 (Fed. Cir. 2015), *cert. denied*, 137 S. Ct. 292 (2016).

IV. CONCLUSION

The '441 patent claims should be found invalid for obviousness.

Date: March 30, 2018

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CERTIFICATE OF COMPLIANCE

This Reply complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 5,597 words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Reply to Patent Owner Response was served on March 30, 2018, via electronic service on lead and back up counsel:

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