UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.,[1]
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737
Patent 7,892,549

PETITIONERS' REPLY TO PATENT OWNER RESPONSE

[1] Pfizer, Inc. is the real-party-in-interest in IPR2017-00737. (Paper 10 at 2.) Samsung Bioepis Co. Ltd.'s IPR2017-01960 has been joined with this proceeding. (IPR2017-01960, Paper 11.) Emphasis is added unless otherwise noted

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I. INTRODUCTION

PO's response merely confirms what the Petition established—that the claimed three-drug treatment is nothing more than the natural result of following the prior art's explicit teachings. PO does not even dispute that the Baselga prior art would have motivated POSAs to combine trastuzumab and paclitaxel for treatment of HER2+ breast cancer treatment in humans. Nor does it dispute that Gelmon taught combining paclitaxel with cisplatin in treatment of metastatic breast cancer, leading to synergistic efficacy improvement. And although PO baldly asserts that Gelmon was "discredited" and would not be considered relevant in treating HER2+ patients, those positions were readily refuted by ***PO's own expert and Dr. Gelmon herself***. PO's criticisms of Gelmon also cannot be reconciled with its inclusion of cisplatin in the laundry list of "further growth inhibitory agents" in the '549 patent for use in the claimed three-drug combination, without providing any further efficacy or safety information than was in the prior art.

That just leaves PO's assertion that POSAs would not have expected success in achieving the claimed efficacy benefit. But according to PO's own positions, that benefit is merely the inherent result of the obvious claimed combination, which cannot establish patentability. Moreover, even if expectation of enhanced efficacy were a requirement here, PO and its expert do not even argue it would not have been expected under the Board's construction, relative to ***untreated patients***.

Finally, even under PO's erroneous construction contradicting its clear prosecution statement—comparing to ***paclitaxel alone***—the claimed efficacy benefit still would have been readily expected by POSAs. Baselga taught that trastuzumab treatment led to "unusually long" time to disease progression in HER2+ patients, while PO and its expert contend that those same patients were believed to "not respond well" to paclitaxel alone. In addition, PO does not even argue, much less show, that addition of a "further growth inhibitory agent," including cisplatin, would have been expected to abrogate that benefit. Nor could it, given the lack of any data for ***any*** claimed three-drug combination in the patent.

The '549 patent Challenged 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¶¶89-90.)

B. "In An Amount Effective To Extend The Time To Disease Progression In The Human Patient" And "An Effective Amount"

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. 3001 at 3-4.) PO represented the

term would be "readily understood" as "relative to an ***untreated patient***." (*Id.* at 17-18.) Dr. Desmond-Hellmann testified "[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.) And 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 that "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 at 4.) But PO omits Dr. Lipton's testimony 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.*) Finally, even if PO's chosen construction "make[s] no sense" (POR 40), it 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¶¶91-94.)

III. ARGUMENT

PO concedes the Baselga prior art would have motivated POSAs to combine trastuzumab and paclitaxel to treat HER2+ breast cancer patients. PO also does not dispute that Gelmon '96 showed synergistic efficacy from the paclitaxel-cisplatin combination in treatment of metastatic breast cancer without undue toxicity, motivating POSAs to further investigate adding additional non-cross-resistant agents in three-drug combinations. And PO does not even argue, much less show, that POSAs would not have expected the claimed clinical efficacy benefit under the Board's construction. That should be the end of this IPR.

PO's contrary arguments amount to nothing more than smoke and mirrors. Given its concession that Baselga '97 would have motivated POSAs to combine trastuzumab with paclitaxel, its arguments regarding alleged lack of motivation to do so in Baselga '96 and '94, that POSAs would have avoided taxoids in favor of anthracyclines, and that the "development history" of Herceptin® shows non-obviousness, fall by the wayside. But they are wrong too, as explained below.

PO's arguments regarding Gelmon '96 fare no better. PO's argument that Gelmon's results would have been discounted because they did not consider HER2+ status of patients were directly refuted by PO's expert and Dr. Gelmon

herself. So too were PO's arguments that Gelmon's results were "not reliable" and "discredited." Indeed, both testified Gelmon's results motivated extensive ongoing investigations of combining cisplatin with paclitaxel for treatment of metastatic breast cancer, ***including with additional agents***.

The claimed efficacy benefit cannot save the claims, as according to PO's own positions it is merely the inherent result of an obvious combination. Moreover, PO and its expert do not even argue, much less show, that benefit would not have been reasonably expected under the Board's construction, as compared to ***untreated patients***. Even under PO's erroneous construction—relative to ***paclitaxel alone***—POSAs reasonably would have expected the claimed efficacy benefit in light of the prior art clinical and preclinical data. Baselga '97 described PO's Phase III trial comparing the trastuzumab/paclitaxel combination to standalone paclitaxel, with extension of time to disease progression ("TTP") compared to paclitaxel alone being a primary endpoint. Named inventor Dr. Desmond-Hellmann described this trial as the "same thing" she relied upon for her invention. (Ex. 1091_142:9-144:16.) She also testified she "wouldn't have done a clinical trial unless [she] thought that the combination would extend time-to-disease progression," and this was "normal" in the field. (*Id.* at 95:8-18.) Moreover, synergistic efficacy had been shown for the trastuzumab-paclitaxel combination in the Baselga '94 study, which would further have enhanced the expectation of achieving extended TTP over

standalone paclitaxel.

Addition of a "further growth inhibitory agent" would not have been expected to abrogate this benefit. Under either party's construction, the claims do not require efficacy benefit from this third agent, and the patent presents no testing of the claimed three-drug combination. In any event, Gelmon taught combining cisplatin with paclitaxel led to synergistic efficacy improvement.

Finally, PO does not argue, much less show, any "objective indicia" support non-obviousness of the claimed treatment.

A. Grounds 1-6: The Baselga References In View Of Gelmon Would Have Motivated Administering The Claimed Combination To Humans.

1. Grounds 1-3: Baselga '97 taught administering the trastuzumab/paclitaxel combination to humans

As PO acknowledges, Baselga '97 "describes the design of the Phase-III study for rhuMAb HER2 after [PO] amended the protocol to allow patients to be treated with the combination of rhuMAb HER2 and paclitaxel." (POR 34; Exs. 1007 at 10; 1087_289:23-292:21, 29:4-296:17.) PO and its expert thus concede that Baselga '97 teaches treating humans with the combination of trastuzumab and paclitaxel. (Ex. 1011¶¶ 77-81; POR 53-60; Ex. 1087_296:18-297:6.)

2. Grounds 4-6: Baselga '96 and '94 also taught administering the trastuzumab/paclitaxel combination to humans

Given PO's concession regarding Baselga '97's teachings, there is no need

to identify equivalent teachings in Baselga '96 and '94 for obviousness. But PO's argument that such teachings are absent (POR 53-54) is meritless.

First, 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. 1005 at 15.) PO also concedes that "such combination therapy" refers to the "same studies disclosed in Baselga '94," which used "rhuMAb HER2 combined with…a taxoid (paclitaxel)." (POR 30, 54.) The only reasonable interpretation is that trials of trastuzumab with paclitaxel (as well as cisplatin and doxorubicin) were "currently in progress." (Exs. 1011¶153; 1085¶126.) PO's expert conceded "[o]ne might interpret it that way, yes." (Ex. 1087_252:20-253:22.) When Baselga '96 was published and read by POSAs, clinical trials of the trastuzumab-paclitaxel treatment ***were*** ongoing. (Exs. 1005 at 9; 2007; 1087_254:03-257:02; *see also* Ex. 1085¶¶124-125, 127-128; Ex. 1086¶¶ 78, 79, 131, 157-158.)[2]

Second, PO's attempts to discredit Baselga '94 (co-published by ***its own researcher***) revise history. POSAs did ***not*** wait for the results to be published in a full, peer-reviewed paper before drawing conclusions from them. (POR 55.)

[2] Petitioner is not relying on "***prior*** systemic [paclitaxel] treatment." (POR 53.)

Rather, Baselga '94 was cited 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; *see also* Ex. 1087_239:2-14.)

PO's criticisms of the design of the Baselga '94 study also fail. For example, PO criticizes the study for being "based on a single cell line" (POR 55-56), but is not even supported by the reference it quotes, which states only that "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*. at 11.) That very same reference, and other references by the same author—Dr. Robert Clarke—make clear that "[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." (Exs. 1074 at 3; 1088_201:22-202:05; 1087_146:7-16; *see also* Exs. 1085¶¶133-135; 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 previously showed response to trastuzumab. (Exs. 1086¶¶61-63, 114; 2065 at 259.) And 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; Ex. 1086¶69.)

PO's criticism of Baselga's "site of implantation"—subcutaneous—fares no better. (POR 12, 56.) Dr. Kerbel conceded that implantation site was "***not a concern*** in the Baselga '94 study," that POSAs "wouldn't have considered the use of subcutaneous implantation to be a design flaw in the Baselga '94 study" and that 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." (Ex. 1088_224:21-225:15, 227:3-228:3; *see also* Exs. 1085¶¶137-139; 1086¶¶69, 70.)

That just leaves PO's general criticisms of preclinical mouse studies. (POR at 7-11.) These criticisms ignore the reality that POSAs ***did*** consider Baselga '94 to be predictive. (Exs. 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* Exs. 2004 at 5; 1085¶¶129-132.) 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 at 7-9 (citing Exs. 2023 (Marsoni ***1984***) and 2075 (Bibby ***1999***); 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.) Notably, 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.) He also admitted his own patent claims antibody-chemotherapy treatments for cancer in humans 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 that Baselga '94's "note" that "clinical studies are underway" is "just a generic reference to clinical trials of rhuMAb HER2." (POR 31.) However, PO provides no support for this interpretation, which makes no 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.*) But PO's investigation, which it does not describe, was not publicly available before the '549 patent's priority date, and does not change Baselga '94's clear statement.

PO never explains why Baselga's mouse studies were conducted if they were truly thought not to be predictive in the first place. 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 that (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. 1086¶77-81.)

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

PO's argument that POSAs would have avoided combining trastuzumab with paclitaxel because of "significant concerns with using taxoids to treat HER2-positive breast cancer" (POR at 17-18, 57-58) is absurd. By 1996, ***paclitaxel was FDA-approved for the treatment of breast cancer*** and was admittedly "one of the most promising treatments for breast cancer." (Exs. 1066; 1036 at 5; 1087_66:11-16, 69:19-70:5.) Paclitaxel was used for ***both*** first and second-line treatments. [redacted] And Baselga '97 already disclosed that the trastuzumab-paclitaxel combination was being tested ***in***

a Phase III clinical study, based on preclinical studies showing *inter alia* that trastuzumab did "not increase the toxicity of paclitaxel." (Exs. 1007 at 10; 1006 at 4; 1005 at 15.) That data from the study was not yet disclosed is irrelevant, as obviousness is shown 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 that "cannot be the proper standard since the expectation of success need only be reasonable, not absolute").

To the extent the Taxol® label warned of adverse events, they were rare and reversible. (Exs. 1066 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 that the Physicians' Desk Reference PO relies on "actually state[d] how to prevent those reactions" and that "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 concluding that "breast cancers that overexpress [HER2] will not respond well to Taxol." (POR at 17, 58; Ex. 2029 at

1362.) But 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 see also* Ex. 1085¶¶146-150.)

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

Any motivation to try the trastuzumab-anthracycline combination (POR at 59-60) 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). And there certainly was motivation to try the trastuzumab-paclitaxel combination without anthracyclines. (Exs. 1006 at 4; 1011¶70.) Indeed, Baselga '97 reported POSAs were doing just that. (Ex. 1007 at 10.)

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 concern, 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¶27; 1042 at 11-12.)[3] 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¶28; 2105 at 6; 1087_32:4-15.) While these concerns may not have led POSAs to abandon anthracyclines altogether, 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

[3] The other identified techniques led to concerns about "whether antineoplastic activity is preserved," and/or had data showing "lower response rates and faster tumor progression times." (Exs. 1042 at 11; 1087_50:18–52:20, 54:9–19.)

cardiotoxic cumulative dose of anthracyclines," with paclitaxel "being one of them." (Ex. 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).

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

PO's reliance on Herceptin®'s "development history"—that it first commenced human trials with ***anthracyclines*** (POR 22-27, 58-59) is misplaced. Baselga '97 already disclosed PO's ***revised*** protocol, including the trastuzumab-paclitaxel arm. (Ex. 1007 at 10.) And if anything, PO's internal documents establish ***obviousness***, as they confirm that the purported concerns PO raises here—"design flaws" in Baselga '94, paclitaxel "resistance" in HER2+ cells, and paclitaxel's toxicity—were not factors in the decision to test the trastuzumab-paclitaxel combination in humans. (Exs. 2002-06.) Nor has PO identified any "unique" insight Dr. Hellmann brought. (POR at 24-26, 58.) Rather,

[redacted] That PO felt confident enough to test the trastuzumab-paclitaxel combination first in Phase III trials reflects the expectation in the field, based on preclinical data, that the combination would be safe and effective. (Ex. 1087_212:7-213:11; *see also* Exs. 1085¶¶128-132; 1086¶¶119-123.)[4]

Notably, PO does not dispute it ***never*** tested the claimed ***three-drug*** combination prior to the '549 patent priority date, relying on ordinary skill to choose the "further growth inhibitory agent." (POR 49; Ex. 1087_283:8-285:10.) Dr. Desmond-Hellmann testified that PO and its collaborators were "debat[ing]" whether to combine trastuzumab with paclitaxel or cisplatin, based on positive preclinical results from combining trastuzumab with ***either*** drug. (Ex. 1091_33:13-37:3, 44:12-46:16, 49:3-51:1, 74:18-76:4.) Combining the three drugs was the next logical step. (Ex. 1085¶40.)

[4] [redacted] PO's expert admitted she was not aware of any data suggesting a "***negative*** result" combining trastuzumab and paclitaxel. (Ex. 1087 at 83:3–18; *see also* Ex. 1091_74:18–77:5.)

6. Gelmon '96 Would Have Motivated POSAs To Add Cisplatin To The Trastuzumab/Paclitaxel Combination

Gelmon '96 would have motivated POSAs to add cisplatin to the known trastuzumab/paclitaxel combination. (PET 22, 27-28, 46-47; Ex. 1011¶¶58-60, 79-81, 153-55.) That Gelmon '96 did not explicitly address HER2+ status (POR at 61) is irrelevant. PO's own expert agreed that "[i]n looking to determine which chemotherapeutic agents to combine with Herceptin," "[POSAs] would look generally to the experience with chemotherapeutic agent treatment ***in metastatic breast cancer generally***" and "that a particular study did not address the HER2-positive status of patients…doesn't mean that it would have been discounted in determining which chemotherapeutic agent to combine with Herceptin." (Ex. 1087_298:4-298:21.) Moreover, in related IPR2017-00804/05, ***Dr. Gelmon herself*** testified that "[t]he body of knowledge we had prior to the approval of trastuzumab was based on an ***agnostic*** treatment of metastatic breast cancer that didn't take into account factors such as HER2 overexpression;" consequently, POSAs "looking to determine how trastuzumab should be dosed" "***would have looked at how we treat metastatic breast cancer generally***." (Ex. 1089_175:8-178:3.)

PO also cannot reconcile its criticism of Gelmon '96 for (in its view) "only" showing "median" TTP and not containing a "control arm" (POR 35) with its own patent's disclosure, which identifies cisplatin among a laundry list of "further

growth inhibitory agents," yet contains no data whatsoever for the claimed three-drug combination, much less data showing it extends TTP. (Ex. 1001_11:4-40.)

Nor was Gelmon's research "discredited." (POR at 61-62.) Even PO's selectively-cited studies do not support it. Wasserheit concluded that "higher doses of both agents per cycle" likely accounted for higher toxicity compared to Gelmon. (Exs. 2068 at 1997; 1087_300:8-23.) Sparano stated lower response rates most likely were due to "the marked imbalance in number of disease sites." (Exs. 2120 at 1884; 1087_300:24-302:23.) And McCaskill-Stevens still showed a relatively high (***60%***) response rate for the paclitaxel/cisplatin combination. (Ex. 2121 at 2.)

PO also ignores other studies where investigators, motivated by Gelmon, combined paclitaxel and cisplatin, including with additional agents. Ezzat found that "[t]he combination of paclitaxel and cisplatin is very effective in metastatic breast cancer" and "toxicity has been acceptable." (Exs. 1081 at 1; 1087_305:6-310:23.) Klaassen, motivated by Gelmon's "promising early results," found paclitaxel combined with cisplatin and a third agent to be "an effective non-anthracycline-containing regimen for the first-line treatment of MBC." (Exs. 1083 at 1, 5; 1087_313:03-314:21.) And Frasci, similarly motivated by Gelmon's "promising results," found weekly paclitaxel-cisplatin to be "an active and particularly well tolerated treatment for patients with either unpretreated or pretreated metastatic breast cancer," concluding that "clinical trials testing ***the***

addition of non cross-resistant drugs to this combination should be performed." (Exs. 1082 at 2; 1087_310:24-313:02.) Notably, Dr. Gelmon testified Frasci was a "follow-on" from Gelmon '96, which "ultimately motivated the Frasci trial." (Ex. 1089_170:25-171:25.)[5] PO relies on Frasci in IPR2017-00804/05 as teaching a regimen POSAs would use in combination with trastuzumab. (IPR2017-00804, Paper 41 at 9, 10, 31.) And based on these studies, PO's clinical expert agreed that "***there was a motivation to add additional drugs to the paclitaxel/cisplatin combination***." (Ex. 1087_314:19-24.)

PO's assertion that prior art taught away from combining trastuzumab with paclitaxel and cisplatin also is undermined by PO's own patent, which includes no data showing ***any*** claimed three-drug combination would have high response rates or acceptable toxicity. Had the state of the art been as PO paints it, PO surely would have needed to include some data supporting its claims rather than rely (as it did) only on its say-so.

Finally, PO and its experts do not dispute that the additional limitations of claims 12 and 13 would have been obvious in light of Drebin '88 and Presta '97,

[5] Perez '98 (Ex. 2124; POR 36) was published after the '549 patent priority date and does not accurately reflect the reality that POSAs ***were*** combining cisplatin and paclitaxel, including with other agents, to treat metastatic breast cancer.

respectively. (*See* POR, Ex. 2062, *generally*.) That means they also do not dispute that adding another HER2 antibody or an anti-VEGF antibody as the "further growth inhibitory agent" would have been obvious. (PET 41-43, 59-61; Ex. 1011¶¶134-141, 211-218.) That is all that is required by all Challenged Claims.

Notably, when the Examiner rejected the '549 patent application for obviousness-type double patenting over the '441 patent application, PO never argued that addition of the "further growth inhibitory agent" rendered the claims patentable; rather, it filed a terminal disclaimer. (*See* Ex. 1019_7:45-65.)

B. Grounds 1-6: The Claimed Clinical Benefit Does Not Establish Patentability

1. The claimed benefit is an inherent result of an obvious combination

In a last-ditch effort to save its claims, PO argues POSAs would not have reasonably expected the claimed clinical benefit. (POR 4-5, 42-53.) But 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 ('TTP') as compared with patients receiving taxoid therapy alone." (*Id.* at 3.) 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.)[6] Moreover, in successfully antedating Baselga '97 in IPR2017-00731, PO similarly argued the claimed benefits naturally flowed from this known combination. (IPR2017-00731, POPR at 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); IPR2017-00731, Ex. 1011_2:239, 310-12.) PO does not argue that addition of a "further growth inhibitory agent" would abrogate this inherent benefit.

It is well-established that inherent results of an otherwise 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); *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("Newly discovered results of known processes directed to the same purpose are not patentable."). Baselga disclosed administration of the trastuzumab-paclitaxel combination to patients. (Exs. 1005 at 15; 1006 at 4; 1007 at 9-10; PET

[6] 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.)

26-27, 44-45.) And there was nothing new about the dosages used in PO's clinical trial. (Exs. 1085¶159; 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 trastuzumab-paclitaxel combination described by Baselga, with the obvious addition of a "further growth inhibitory agent" that would not have been expected to adversely impact the anticipated clinical benefit. *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) cannot establish patentability. *Id.*; *see also* Ex. 1085¶¶157-159.

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 contend that extended TTP compared to ***untreated*** patients under the Board's construction would have been unexpected. (POR 42-53; Ex. 1087_274:5-275:08.) 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***" (with the same results reported in Baselga '97), while PO and its expert contend that HER2+ patients were believed to "***not respond well***" to standalone paclitaxel. (Exs. 1005 at 9, 13; 1007 at 9; POR 17, 22, 23, 58; Ex.

2062¶57.) Baselga '97 also described PO's Phase III trial comparing the trastuzumab/paclitaxel combination to standalone paclitaxel, with extension of TTP compared to paclitaxel alone being a primary endpoint. (Ex. 1007 at 10.) Dr. Desmond-Hellmann confirmed that the trial was the "same thing" she relied upon for her "invention." (Ex. 1091_142:9-144:16.) Also, she "wouldn't have done a clinical trial unless [she] thought that the combination would extend time-to-disease progression." (*Id.* at 95:8-18.) That was "normal" for people "who are in the business of conducting clinical trials." (*Id.*)

This expectation of efficacy benefit would have been bolstered by the reports in Baselga '97, '96 and '94 of synergistic preclinical cytotoxicity of the trastuzumab-paclitaxel combination—the best of any tested—leading to "clinical trials." (Exs. 1006 at 4; 1007 at 9; 1005 at 15; 1088_84:17-85:11.) Although Baselga '94 reported ***response rate*** (*i.e.*, shrinking tumors), that was a widely-used "surrogate endpoint" for TTP in preclinical trials. (Exs. 1080 at 3-4; 1085¶¶53, 77, 99, 163; 1086¶¶132-36, 162.)

Finally, PO does not contend that adding a third drug would have been expected to abrogate that expected benefit. (POR at 49.) Although PO argues that Gelmon '96 includes "no comparative data showing any ***extension*** in TTP" for the paclitaxel/cisplatin combination (POR at 46-47, 51), the claims do not require addition of cisplatin itself to yield any clinical benefit. (Ex. 1085¶164.) Nor was

the Gelmon '96 teaching "undermine[d]," as discussed above (*See* Section A.6, *supra*.)

C. Grounds 1-6: The Claimed Combination Would Have Been Obvious To Try

In view of the prior art, POSAs at least would have found the claimed combination obvious to try. (PET 62-63; Ex. 1011¶¶85, 160.) PO argues that breast cancer patients had been treated with a "host of other breast cancer therapies." (POR 62-63.) Yet, at the time, only ***four*** trastuzumab therapies had been proposed and tested: (i) standalone; (ii) with paclitaxel; (iii) with anthracycline; and (iv) with cisplatin. (Ex. 1085¶177.) The trastuzumab-paclitaxel combination was the ***most effective*** in published preclinical studies, while the trastuzumab-cisplatin and paclitaxel-cisplatin combinations also showed promising results. (*Id.*; Exs. 1005 at 4; 1006 at 15; 1007 at 8-10; 1013 at 5.) It cannot legitimately be suggested that combining the best known options was non-obvious.

PO's argument regarding purported "unpredictability" in the field based on the general failure rate in clinical studies (POR 64) also fails. The Federal Circuit has rejected generalized arguments asserting that 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 a 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, a claimed treatment could never be obvious absent disclosed Phase III results. That is not the law. *In re Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1998) ("Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice."); *see also* Exs. 1085¶¶148-153; 1086¶¶148-153.

D. Grounds 2, 3, 5 And 6: The Additional Limitations Of Claims 12 and 13 Are Obvious Over Drebin '88 And Presta '97

Petitioner previously explained why the limitations of claims 12 and 13 are obvious over Drebin '88 and Presta '97, respectively. (PET 41-43, 59-61; Ex. 1011¶¶ 134-41, 211-218.) PO does not respond, and does not contend the limitations of claims 12 and 13 are non-obvious. (POR 36-37; Ex. 2062¶¶173-76.)

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

PO and its expert identify no "objective indicia" of non-obviousness. (Ex. 1087_316:21-317:10.) Nor could they, as there is no evidence PO tested the claimed combination. (*Id.*_283:17-285:10.) PO refers to the Sliwkowski prosecution declaration (POR 39), but Petitioner previously explained why that does not assist PO. (PET 61-65; Ex. 1011¶¶219-28.) In response, PO submits only "naked attorney argument," which is "insufficient." *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

F. These Proceedings Are Constitutional

This IPR is constitutional. *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1288-93 (Fed. Cir. 201), *cert. denied*, 137 S. Ct. 292 (2016).

IV. CONCLUSION

The '549 patent Challenged 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 5598 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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