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Paper 29
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

PHARMACYCLICS LLC,
Patent Owner.

IPR2019-00865
Patent 9,795,604 B2

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining Some Challenged Claims Unpatentable
Denying in Part and Dismissing in Part Motion to Strike
35 U.S.C. § 318(a); 37 C.F.R. § 42.5; 37 C.F.R. § 42.20

I. INTRODUCTION

Sandoz Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of U.S. Patent No. 9,795,604 B2 (Ex. 1001, "the '604 patent").[1] Paper 2 ("Pet."). Pharmacyclics LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 (Prelim. Resp.).[2] We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Petitioner would prevail in showing that at least one of the challenged claims was unpatentable over the cited art. Pursuant to 35 U.S.C. § 314, the Board instituted trial on September 26, 2019. Paper 8 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Response to the Petition (Paper 13, "PO Resp."), Petitioner filed a Reply to Patent Owners' Response (Paper 17, "Reply"), and Patent Owner filed a Sur-Reply (Paper 24, "Sur-Reply"). With our prior authorization, Patent Owner filed a Motion to Strike Improper Reply Arguments (Paper 25, "Mot."), Petitioner filed an Opposition to Patent Owner's Motion to Strike (Paper 26, "Mot. Opp."), and Patent Owner filed a Reply in Support of its Motion to Strike (Paper 27, "Mot. Reply").

On March 21, 2019, the parties presented arguments at an oral hearing. The transcript of the hearing has been entered into the record. Paper 28 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on

[1] Petitioner identifies Sandoz Inc. and Lek Pharmaceuticals D.D. as the real parties in interest. Pet. 2.
[2] Patent Owner identifies Pharmacyclics LLC, AbbVie Inc, and Janssen Biotech, Inc. as the real parties in interest. Paper 4, 1.

the record before us, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that claims 1, 6–10, 24, 35, 39, and 55 of the '604 patent are unpatentable, but that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 4, 13, 15, 28–31, 43–46 and 50–53 are unpatentable. We deny in part and dismiss in part Patent Owners' Motion to Strike.

A. Related Proceedings

Petitioner and Patent Owner represent that the '604 patent was asserted in *Pharmacyclics LLC v. Zydus Worldwide DMCC*, Civ. No. 1:18-cv-00275-CFC (D. Del.), which has been consolidated with *Pharmacyclics LLC v. Fresenius Kabi USA, LLC*, 1:18-cv-00192-CFC (D. Del). Pet. 2; Paper 4, 1. Petitioner and Patent Owner also represent that U.S. Patent Application No. 15/586,058, filed May 3, 2017, is related to the '604 patent. Pet. 2; Paper 4, 1.

B. The '604 Patent (Ex. 1001)

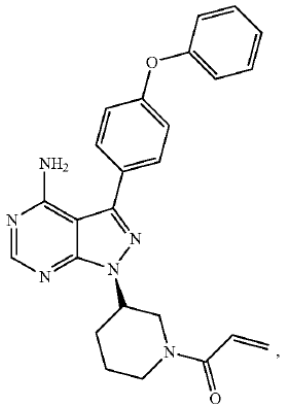
The '604 patent issued October 24, 2017, identifying John C. Byrd, Jason A. Dubovsky, Natarajan Muthusamy, Amy Jo Johnson, and David Miklos as inventors. Ex. 1001, at codes (45), (72). The patent teaches:

> Chronic graft versus host disease (cGVHD) is the most common long-term complication following allogeneic stem cell transplant (SCT), affecting 30-70% of patients who survive beyond the first 100 days. cGVHD and its associated immune deficiency have been identified as a leading cause of non-relapse mortality (NRM) in allogeneic SCT survivors.

Id. at 1:29–36. The '604 patent discloses "methods for treating and preventing graft versus host disease using . . . an ACK inhibitor such as ibrutinib." *Id.* at Abstract.

C. Challenged Claims

Petitioner challenges claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent. Claim 1 is representative and is reproduced below:

> 1. A method of treating chronic graft versus host disease (GVHD) comprising administering to a patient having chronic GVHD a therapeutically effective amount of a compound of the structure:
>
> 
>
> thereby treating the chronic GVHD in the patient.

Ex. 1001, 75:41–68.

D. Prior Art and Asserted Grounds

We instituted trial based on each challenge to the patentability of the '604 patent presented in the Petition. The Petition challenged the patentability of claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent on the following grounds:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	102	The '085 publication[3]
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	103	The '085 publication
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	103	The '085 publication, Shimabukuro-Vornhagen,[4] Herman[5]
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	103	The '085 publication, Shimabukuro-Vornhagen, Uckun[6]

Pet. 30–31.

Petitioner submits the Declaration of Dr. James L. Ferrara (Ex. 1006) in support of the Petition. Patent Owner submits the Declaration of Dr. John Koreth (Ex. 2055) in support of its Response to the Petition.

E. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in

[3] Goldstein, US Patent Publication No. 2015/0140085 A1, published May 21, 2015 (Ex. 1002, "the '085 publication").
[4] Shimabukuro-Vornhagen, et al., *The Role of B Cells in the Pathogenesis of Graft-Versus-Host Disease,* 114(24) BLOOD 4919–4927 (2009) (Ex. 1003, "Shimabukuro-Vornhagen").
[5] Herman, et al., *Bruton Tyrosine Kinase Represents a Promising Therapeutic Target for Treatment of Chronic Lymphocytic Leukemia and is Effectively Targeted by PCI-32765,* 117(23) BLOOD 6287–6296 (2011) (Ex. 1004, "Herman").
[6] Uckun, et al., *Bruton's Tyrosine Kinase as a Molecular Target in Treatment of Leukemias and Lymphomas as well as Inflammatory Disorders and Autoimmunity,* 20(11) EXPERT OPIN. THER. PATENTS 1457–1470 (2010) (Ex. 1005, "Uckun").

the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros*.).

Petitioner contends that the person of ordinary skill "would have had an advanced degree in the field of medicine with additional, specialized training, such as a fellowship in Hematology/Oncology as well as several years' experience specializing in transplantation." Pet. 31; Ex. 1006 ¶¶ 53. Petitioner also contends that the POSA would "preferably have had some experience with pharmaceutical compositions for treating GVHD or related conditions." Pet. 31–32.

In our Institution Decision, we accepted Petitioner's definition of the POSA. Inst. Dec. 5–6. Patent Owner does not challenge the definition set forth by Petitioner and adopted in our Institution Decision. *See generally* PO Resp, Sur-Reply. The fully developed trial record supports that this definition is consistent with the level of skill reflected in asserted prior art references and in the '604 patent. Accordingly, in this decision, we apply Petitioner's definition of the POSA.

F. Claim Construction

We construe claims "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37

C.F.R. § 42.100(b) (2019)). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp*., 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would have been 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. *Id.* Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

Patent Owner requests that we construe what it terms "efficacy limitations" in claims 6, 7, 8, 29, 30, 31, 44, 45, 46, 51, 52, 53, and 55. PO Resp. 5–16. These limitations recite particular patient outcomes resulting from the administration of ibrutinib in dependent claims 6, 7, 8, 29, 30, 31, 44, 45, 46, 51, 52, and 53. The particular patient outcomes recited in these dependent claims are summarized in the Table below.

Dependent Claims	**Text of limitations**
6, 29, 44, 51	"wherein, following administration of the compound, the patient achieves partial response (PR), wherein the PR is an objective response in one involved organ in the patient with no evidence of progression elsewhere and no requirements for additional systemic therapy."

Dependent Claims	Text of limitations
7, 30, 45, 52	"wherein, following administration of the compound, the patient achieves complete response (CR), wherein the CR is a complete restoration of symptoms attributable to GVHD."
8, 31, 46, 53	"wherein, following administration of the compound, the severity of the GVHD is reduced."

Patent Owner also requests that we construe the terms "method of treating," which is recited in claims 1 and 55, and the limitation "thereby treating the chronic GVHD in the patient," which is recited in claim 1. PO Resp. 6.

In its Petition and in its Reply, Petitioner argues that these claim limitations merely state the result of performing the method set forth in the claim and add nothing to the patentability or substance of the claim. Pet. 40; Pet. Reply 2. Accordingly, Petitioner contends that these limitations are not entitled to patentable weight. *Id.* Patent Owner contends that the recited patient outcomes should be given patentable weight because they "are material to patentability and express the inventive aspect of the claimed invention." PO Resp. 6.

Although the parties dispute the proper claim construction of these claim terms, we determine that no explicit construction of these terms is necessary to resolve this dispute because, as discussed *infra* 11–12 and 27–30, we find that these limitations are inherently present in the cited art. *See Nidec*, 868 F.3d at 1017 ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs.*, 200 F.3d at 803)); *Wellman, Inc. v. Eastman Chem.*

Co., 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy'").

II. GROUND 1: ANTICIPATION BY THE '085 PUBLICATION

Petitioner asserts that the '085 publication anticipates claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent. Pet. 34–44. Patent Owner opposes. PO Resp. 16–21, 53–56. We have reviewed Petitioner's and Patent Owner's assertions, as well as the evidence of record, and, for the reasons discussed below, we conclude that Petitioner has demonstrated by a preponderance of the evidence, that claims 1, 6–10, 24, 35, 39, and 55 of the '604 patent are anticipated by the '085 publication, but that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 4, 13, 15, 28–31, 43–46 and 50–53 are anticipated by the '085 publication.

A. Disclosures of the Asserted Prior Art

The '085 Publication

The '085 publication discloses "[o]ral pharmaceutical formulations of ibrutinib . . . and use of these formulations for the treatment of diseases treatable by ibrutinib such as . . . autoimmune diseases." Ex. 1002, Abstract. Among the autoimmune diseases disclosed as treatable using the oral pharmaceutical formulations of the '085 publication is graft versus host disease. *Id.* ¶ 98 ("In another embodiment of this aspect, the patient in need is suffering from a heteroimmune condition or disease, e.g., graft versus host disease."). According to the '085 publication, "[t]he therapeutically effective amount of ibrutinib . . . can be from about 20 mg per day to about 450 mg/day, or 20 mg/day to about 420 mg/day; or about 20 mg/day or 30 mg/day to about 300 or 350 mg/day; or about 30 or 50 mg/day to about 200,

or 220 or 250 mg/day; or about 30 or 50 mg/day to about 100 or 150 mg/day and can be administered in single or multiple doses." *Id.* ¶ 30.

B. Analysis

Claim 1

Petitioner contends that the '085 publication discloses all of the limitations of claim 1. Petitioner acknowledges that the '085 publication discloses treating graft versus host disease rather than chronic graft versus host disease, as claimed. Pet. 35. However, Petitioner contends that there are only two types of graft versus host disease – chronic and acute. *Id.* Supported by the testimony of Dr. Ferrara, Petitioner asserts that a POSA would have "at once envisaged that this disclosure pertains to both acute and chronic GVHD." *Id.* (citing Ex. 1006 ¶ 77). Petitioner thus contends that the '085 publication anticipates treatment of chronic GVHD. *Id.* Petitioner cites *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012) and *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) as supporting the proposition that a species within a genus is anticipated where the genus was of "such a defined and limited class that one of ordinary skill in the art could 'at once envisage' each member of the genus." Pet. 35.

With respect to the requirement of claim 1 for "administering . . . a therapeutically effective amount," Petitioner points to the disclosure in the '085 publication of "therapeutically effective" amounts of ibrutinib. Pet. 36–37 (citing Ex. 1002 ¶¶ 30, 120). Petitioner argues that the term "therapeutically effective amount" in claim 1 must encompass the amounts

recited in claim 5, which depends from claim 1, and which recites amounts corresponding to those disclosed in the '085 publication. *Id.* at 14.

With respect to the "thereby treating the chronic GVHD in the patient" recitation in claim 1, Petitioner argues that to the extent it is limiting, the '085 publication discloses it both expressly and inherently. *Id.* at 37.

Based on the arguments and evidence presented during this review, we find that Petitioner has shown by a preponderance of the evidence that the '085 publication discloses each and every limitation of claim 1 of the '085 publication. As discussed above, the '085 publication discloses treatment of GVHD. *See supra* p. 9. Although, the '085 publication does not specify whether such GVHD is chronic or acute, Petitioner provides evidence that there are only two types of GVHD, acute and chronic. Ex. 1006 ¶ 29 (cited at Pet. 7). Accordingly, we understand the '085 publication's reference to GVHD to disclose a genus comprised of acute and chronic GVHD. Petitioner offers the testimony of Dr. Ferrara, which we credit as supported by the record, that the POSA, "upon seeing the '085 Publication's disclosure directed to treating 'graft versus host disease,' . . . would have immediately understood and envisioned that the '085 Publication's disclosure of treating GVHD includes specifically ***chronic*** GVHD." *Id.* ¶ 77. The trial record thus supports that the POSA would have understood the '085 publication to disclose treatment of chronic GVHD.

The trial record also supports that the '085 publication discloses administration of a therapeutically effective amount of ibrutinib. Ex. 1002 ¶¶ 30, 120; Ex. 1006 ¶¶ 78–82. And, to the extent the recitation "thereby treating the chronic GVHD in the patient" is considered to limit

claim 1, the '085 publication discloses such treatment (Ex. 1002 ¶¶ 94, 98, 117–120) and the trial record supports that administration of a "therapeutically effective amount" of ibrutinib will inherently "treat" cGVHD (Ex. 1006 ¶ 83; *see also,* Ex. 1001, 26:47–53 ('604 patent defining the term "treating" broadly)).

Patent Owner no longer disputes that the '085 publication teaches treatment of cGVHD, but instead argues that the '085 publication does not anticipate the '604 patent because it does not enable treatment of cGVHD with ibrutinib. PO Resp. 53–56.[7] More specifically, Patent Owner argues that the '085 publication does not enable treatment of cGVHD "because of its lack of guidance and working examples in an exceedingly unpredictable field." PO Resp. 53. According to Patent Owner, cGVHD was "poorly understood" and "widely recognized as an unpredictable disease that was exceedingly difficult to treat." *Id.* Research on cGVHD was hampered by the absence of "adequate animal models or reliable biomarkers" and "the field was inundated with unreliable studies." *Id.* Patent Owner contends that, as a result, "the prior art recognized that the 'trial-and-error system' was the 'only way' to identify drugs effective for cGVHD." *Id.* at 53–54.

[7] In its Preliminary Response, Patent Owner also argued that the '085 publication did not anticipate claim 1 because it did not disclose treatment of chronic GVHD and because Petitioner's anticipation arguments required picking and choosing among disclosures. Prelim. Resp. 38–41. These arguments are waived because Patent Owner did not pursue them in its post-institution briefing. *See* Paper 9, 7 ("Patent Owner is cautioned that any arguments for patentability not raised in the response may be deemed waived."). Even if we were to consider these arguments, we would find them unpersuasive for the reasons set forth in our Institution Decision at 14–16.

Against this backdrop, Patent Owner contends that the '085 publication provides insufficient guidance to enable the POSA to practice the claimed invention. *Id.* at 31. Patent Owner explains:

> [T]he '085 Publication contains no *in vitro*, preclinical, or clinical data indicating that ibrutinib could treat cGVHD, which it fails even to mention. EX2055, ¶¶124–130. The '085 Publication is devoid of working examples for treating *any* disease. *See generally* EX1002. Instead, each of the six examples (five of which are prophetic) relates to formulations untethered to treating any particular disease. *Supra* § VI.A.1. The text of the '085 Publication likewise provides no guidance for treating cGVHD. Instead, "graft versus host disease" is generically identified among over 150 diseases. EX1002, [0096]–[0100]. Although the '085 Publication provides generalized disclosures about "therapeutically effective amounts," that disclosure does not specify any particular disease and is taught to "vary depending on the compound, the disease and its severity[,] and the age, weight, etc. of the mammal to be treated." *Supra* § VI.A.1; EX1002, [0030], [0120]. In other words, while teaching that many factors must be considered to determine a "therapeutically effective amount" for a particular disease, the '085 Publication provides no guidance as to how one would effectively treat cGVHD, especially against the backdrop of unpredictability in this field. EX2055, ¶¶121–122.

PO Resp. 54–55. We are not persuaded.

Prior art publications and patents are presumed to be enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Here, the '085 publication discloses "[o]ral pharmaceutical formulations of ibrutinib and/or a pharmaceutically acceptable salt thereof." Ex. 1002, Abstract. It also discloses that these formulations may be used to treat a patient "suffering from a heteroimmune condition or disease, e.g., graft

versus host disease" (*id.* ¶ 98) by "administering to the patient . . . a solid oral dosage form disclosed herein." *Id.* ¶ 96.

We acknowledge Patent Owner's argument that the '085 publication does not include instructions specific to cGVHD. However, per claim 1, all that is required to treat cGVHD is to administer a therapeutically effective dose of ibrutinib, which the '085 publication teaches. Ex. 1001, 75:40–67 (claim 1); *see also,* Tr. 37–38 (MR. RAICH: ". . . The '085 Publication as I mentioned earlier, has no guidance whatsoever in terms of how to treat the disease . . . . JUDGE COTTA: What guidance is needed beyond just identifying a dose? MR. RAICH: I would say a dose and a dosing regimen would be an appropriate thing to provide in terms of how to actually treat the disease.").

The '085 publication provides general guidance – not specific to any one disease – on administering therapeutically effective doses of ibrutinib and on the frequency with which those doses should be administered. In describing one of the disclosed solid oral dosage forms, it states:

> The therapeutically effective amount of ibrutinib and/or a pharmaceutically acceptable salt thereof when administered into the intestine by bypassing the stomach can be from about 20 mg per day to about 450 mg/day, or 20 mg/day to about 420 mg/day; or about 20 mg/day or 30 mg/day to about 300 or 350 mg/day; or about 30 or 50 mg/day to about 200, or 220 or 250 mg/day; or about 30 or 50 mg/day to about 100 or 150 mg/day and can be administered in single or multiple doses.

Ex. 1002 ¶ 30; *see also, id.* ¶26. Similarly, in defining the term "therapeutically effective amount," the '085 publication teaches:

> The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. The therapeutically effective amount of ibrutinib and/or a pharmaceutically acceptable salt

> thereof when administered in the intestine can be from about 20 mg per day to about 450 mg/day, or any permu[t]ations and combinations thereof. Such as 20 mg/day to about 420 mg/day; or about 20 mg/day or 30 mg/day to about 300 or 350 mg/day; or about 30 or 50 mg/day to about 200, or 220 or 250 mg/day; or about 30 or 50 mg/day to about 100 or 150 mg/day and can be administered in single or multiple doses.

Id. ¶ 120. The doses described in the '085 publication correlate with those identified as "therapeutically effective" in the '604 patent. *Compare id.* ¶¶ 30, 120 with Ex. 1001, 76:7–10 (claim 5).

Patent Owner, through the testimony of Dr. Koreth, observes that the '085 publication provides "no dose or doses of ibrutinib as part of [the] eighth aspect for treating any particular disease, including GVHD." Ex. 2055 ¶ 125. Dr. Koreth also testifies the '085 publication's disclosure of a "therapeutically effective amount" of ibrutinib "is insufficient to provide any information about a therapeutically effective dose of ibrutinib to treat cGVHD, especially as the prior art does not disclose any ibrutinib dose for the treatment of patients with cGVHD." *Id.* ¶ 126. We do not find this persuasive.

We find that the POSA would readily have connected the disclosure in the '085 publication that in an "eighth aspect of the present disclosure" ibrutinib can be used to treat GVHD with the disclosure of dosages of ibrutinib provided in elsewhere in the '085 publication. In this regard, we note that the "eighth aspect" is directed to treating an autoimmune disease, including GCHD, by "administering . . . a solid oral dosage form disclosed herein," and the "solid oral dosage form[s] disclosed" in the '085 publication specify doses of ibrutinib and frequency of administration. *See, e.g.,* Ex. 1002, ¶¶ 26 (identifying ranges of dosages for a "forth aspect" of the present disclosure, which aspect was previously described as providing a "solid oral

dosage" form); 30 (same), 96 (disclosing treatment of autoimmune disease by administering "a solid oral dosage form disclosed herein" as an eighth aspect of the present disclosure), 98 (specifying that the autoimmune disease is graft versus host disease). We are persuaded that the POSA would have understood the "solid oral dosage form disclosed herein" (*id.* ¶ 96) to include the solid oral dosage forms disclosed the "forth aspect" of the disclosure of the '085 patent (*id.* ¶¶ 26, 30), particularly as those doses are consistent with the doses described as being therapeutically effective (*id.* ¶ 120). *KSR Intern. Co. v. Teleflex Inc.,* 550 U.S. 398, 421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

For similar reasons, we are not persuaded that, as Dr. Koreth seems to suggest, a POSA would have required a statement specific to ibrutinib in order to connect the teaching of the '085 patent to treat GVHD with the disclosure of therapeutically effective amounts of ibrutinib. Ex. 2055 ¶ 126; Ex. 1002 ¶¶ 98, 120; *see also* Ex. 1006 ¶¶ 96–101 (Dr. Ferrara testimony on what the POSA would have understood from the disclosure of the '085 publication regarding dosing). Rather, we find that a POSA would naturally have connected the teaching of treating GVHD with the disclosed therapeutically effective amounts of ibrutinib.

In sum, the record does not support a conclusion that a POSA, provided with both information regarding therapeutically effective amounts of ibrutinib and the teaching that ibrutinib can be used to treat GVHD, would have required undue experimentation to carry out the claimed method by selecting a patient appropriate ibrutinib dosage based on age, weight, and other disclosed parameters. Indeed, it is not clear that the POSA would have required any experimentation, much less undue experimentation, as all that

is required to carry out the claimed method is to do what the '085 publication suggests – administer a therapeutically effective amount of ibrutinib.

We acknowledge Patent Owner's argument that cGVHD is a poorly understood, unpredictable disease, and that the prior art relied on trial-and-error to identify drugs effective for cGVHD. However, we are not persuaded that these difficulties, and the other difficulties identified by Patent Owner in its briefing (see PO Resp. 53–56), are sufficient to rebut the presumptively enabled teaching of the '085 publication that ibrutinib can be used to treat GVHD. In this regard, we are guided by our reviewing court's decision in *Rasmussen v. SmithKline Beecham Corp.* 413 F.3d 1318 (Fed. Cir. 2005). The issue in *Rasmussen* was whether the disclosure of a prior art reference, EP '383, enabled the use of finasteride to treat prostate cancer so as to anticipate the patent at issue. *Id.* at 1325–1326. The Board made several findings akin to those argued by Patent Owner here. Specifically, it found:

> (1) that in light of the state of the art at the time of the publication of EP '383 in 1988, there was no reasonable scientific basis for a person of ordinary skill in the art to conclude that the claimed method would be effective in treating prostate cancer, and (2) that given the lack of proof provided in the publication itself, a person of ordinary skill in the art as of the publication date of EP '383 would not have believed that the method described in EP '383 would be effective.

Id. at 1326. Our reviewing court found that these findings were "insufficient to support the Board's conclusion that EP '383 is not an enabling reference for purposes of anticipation." *Id; see also, Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.,* 246 F.3d 1368, 1370, 1378 (Fed. Cir. 2001) (finding that prior art reference anticipated a claim directed to a "method for

reducing hematologic toxicity in a cancer patient undergoing [t]axol treatment comprising parenterally administering to said patient an antineoplastically affective amount of . . . taxol" even though the reference showed that carrying out the method lacked efficacy).

Patent Owner relies on *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.,* 545 F.3d 1312 (Fed. Cir. 2008) to support its argument that the '085 publication does not enable the method it discloses. PO Resp. 55–56. *Impax,* however, is readily distinguishable. In *Impax,* our reviewing court found that a prior art reference did not enable the use of riluzole to treat ALS where: 1) "nothing in [the prior art reference] would direct one skilled in the art to recognize that riluzole could be used to treat ALS," 2) the "dosage guidelines [were] broad and not specific to any of the hundreds of formula I compounds of the claimed invention or to any of the listed diseases," and 3) the prior art reference "tie[d] the dosing information to 'the compounds of the invention' and specifically exclude[d] riluzole from the invention." *Id.* at 1315. Here, the '085 publication specifically teaches that ibrutinib can be used to treat GVHD (Ex. 1002 ¶ 98), and limits its disclosure to one compound, ibrutinib, rather than the hundreds of compounds encompassed by the disclosure in *Impax*. Moreover, there is nothing in the '085 publication remotely equivalent to *Impax's* specific exclusion of riluzole from the invention. We acknowledge that the dosage guidelines in the '085 publication are, like those in *Impax,* not specific to any one disease. However, they are specific to ibrutinib and, as discussed above, we find that the POSA would have connected the dosage guidelines with the teaching that ibrutinib could be used to treat GVHD.

Accordingly, because the '085 publication discloses all of the elements in the method of claim 1, and because Patent Owner has not rebutted the presumption that the '085 publication is enabled, we find that the preponderance of the evidence supports that the '085 publication anticipates claim 1 of the '865 patent.

Claims 4, 13, 15, 28–31, 43–46, and 50–53

Claims 4, 13, and 15 depend from claim 1 and provide additional limitations concerning the patients to whom ibrutinib is administered. Claim 4 specifies that "the patient has steroid-dependent/refractory chronic GVHD." Claim 13 specifies that "the chronic GVHD is steroid resistant GVHD." And claim 15 specifies that "the chronic GVHD is refractory GVHD." Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15.

Petitioner contends that the '085 publication anticipates treatment of such patients because a POSA "would have known that post-steroid treatments – including administering ibrutinib – were started only if steroids were not being effective." Pet. 38–39 (citing Ex. 1006 ¶ 86).

Patent Owner argues that Petitioner improperly relies on the knowledge of the POSA to supply the missing elements of treating steroid-dependent/refractory, steroid-resistant, and refractory cGVHD. PO Resp. 21. Patent Owner contends that "nothing in the '085 Publication discloses whether ibrutinib would be used before, after, or during steroid therapy" nor does it "recognize any of the many variations, in terms of patient subset and disease classification, that identifies the claimed treatment in steroid

resistant/refractory patients." *Id.* (citing Ex. 2055 ¶¶ 135–137). We agree with Patent Owner.

The Petition does not identify any disclosure in the '085 publication of using steroids to treat GVHD. Nor does the Petition identify any disclosure in the '085 publication of whether ibrutinib is a first or second line treatment, instead relying impermissibly on the knowledge of the POSA to supply the limitations recited in these claims. Pet. 38–39. Accordingly, the Petition does not establish by a preponderance of the evidence that the '085 publication anticipates claims 4, 13, and 15. *Nidec Motor Corporation v. Zhongshan Broad Ocean Motor Co. Ltd.,* 851 F.3d 1270, 1274–75 (Fed. Cir. 2017) ("*Kennametal* does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them.").

In addition, beyond Petitioner's improper reliance on the knowledge of the POSA, we are not persuaded as a factual matter that a POSA would have looked at the bald disclosure in the '085 publication of treatment of GVHD with ibrutinib and immediately envisioned from that disclosure that ibrutinib would be used as a second line treatment and in instances where treatments with steroids had failed. *See* Ex. 1006 ¶ 86 (Ferrara testimony to this effect). While we recognize that steroids were generally accepted as a first line treatment, the record supports a desire to find new first line treatments. Ex. 2019, 5074 ("Long-term glucocorticoid treatment causes numerous complications, including infections, myopathy, avascular necrosis, osteoporosis, glucose intolerance, hypertension, growth retardation in children, weight gain, changes in body habitus, cutaneous atrophy and striae, cataracts, emotional lability, and interference with sleep. Development of

less toxic treatments that could reduce the dose or duration of glucocorticoid administration or improve disease control would be of enormous benefit for patients with chronic GVHD."); Ex. 1006 ¶ 33 (Ferrara testimony: "While steroids are the primary treatment for chronic GVHD, they are often ineffective."). Indeed, the evidence supports that those of skill in the art continued to investigate and use drugs as first line treatments even though steroids were generally accepted in that role. Ex. 2019, abstract (investigating whether "the addition of mycophenolcate mofetil (MMF) improves the efficacy of initial systemic treatment of chronic graft-versus-host disease"); Ex. 2001, 49 ("A combination regimen of ciclosporin [a calcineurin inhibitor] and prednisolone may have a steroid-sparing effect and reduce the incidence of steroid-associated complications."); Ex. 2055 ¶ 33 (Dr. Koreth testimony: "It was not uncommon for calcineurin inhibitors (cyclosporine tacrolimus) to be used in combination with corticosteroids as a first line treatment approach").

In addition, steroid-dependent/refractory, steroid-resistant, and refractory cGVHD patients were recognized as "particularly difficult to treat." Ex. 2055 ¶ 137; *id* ¶ 38 (Dr. Koreth's well supported testimony summarizing the prior art as recognizing "steroid-dependent/refractory, steroid-resistant, or refractory cGVHD patients were very hard to treat."); *id.* ¶¶ 35–37 (discussing unsuccessful attempts to treat such patients); *id.* ¶¶ 174–180 (discussing safety concerns for drugs, like ibrutinib, that target B and T cells when administered to steroid-dependent/ refractory, steroid-resistant, or refractory cGVHD patients); Ex. 2056, 124:7–11 (Dr. Ferrara testimony: "So in that sense, a patient with chronic GvHD, particularly one who is being treated for chronic GvHD [i.e. treated with steroids], has an

immune system that is less than that of a newborn baby. Less effective or less protective than that of a newborn baby."); Ex. 2059, 207 (stating that "[t]here are major challenges to developing therapy for cortico-steroid-resistant cGVHD" and identifying some of these challenges). In view of these difficulties, it is difficult to credit Dr. Ferrara's testimony that the POSA would look at the disclosure of treating GVHD in the '085 publication and immediately envision that it discloses treatment of these challenging patients. Ex. 1006 ¶ 86 (Dr. Ferrara testimony on this issue); Ex. 2055 ¶¶ 133–138 (Dr. Koreth testimony on the scope of what is encompassed by "GVHD" and the difficulties in treating the claimed patient population).

For these additional reasons, the Petition does not establish by a preponderance of the evidence that the '085 publication anticipates claims 4, 13, and 15.

In its Reply, Petitioner cites to Dr. Ferrara's testimony in his deposition that the drugs listed in paragraph 124 of the '085 publication are "all steroids that we use to treat Graft-versus-host disease." Reply 9.[8] Petitioner then points to the disclosure in the '085 publication that "other drug(s) may be administered . . . contemporaneously or sequentially with a compound of the present disclosure" (Ex. 1002 ¶ 121) and argues that this

[8] Contrary to the statement in Petitioner's Reply, not all of the drugs listed in paragraph 124 are steroids. Paragraph 124 also includes: "non-steroidal anti-inflammatory drugs," "immunosuppressants," "Cox-2-specific inhibitors," "TNF-alpha binding proteins," "allergy vaccines," "antihistamines," "antileukotrienes," "beta-agonists," "anticholinergics," and a host of other drugs. Ex. 1002 ¶ 124. This is consistent with Dr. Ferrara's deposition testimony, which appears to identify only the glucocorticoids specifically listed in paragraph 124 as "steroids that we use to treat Graft-versus-host disease." Ex. 2056, 210:25–212:7.

teaches that "ibrutinib was disclosed as being given sequentially with steroids, such as when steroids are ineffective" (Pet. Reply 10). Patent Owner moves to strike this on the basis that it presents new argument. Mot. 1. We agree that Petitioner has presented a new argument, and do not consider it for that reason. We address Patent Owner's motion to strike *infra.* p. 65–66.

The Petition relied on the theory, shown through the knowledge of the POSA rather than a disclosure in the '085 patent, that the POSA would have at once envisaged administration of ibrutinib to the claimed patient populations. Pet. 38–39 ("[A] POSA would have known that steroids are universally given as first-line treatment . . . . A POSA likewise would have known that post-steroid treatments—including administering ibrutinib—were started only if steroids were not being effective."); *see also,* Ex. 1006 ¶¶ 32, 86 (Dr. Ferrara's testimony, cited in the Petition). Neither the Petition nor Dr. Ferrara's declaration make any reference to paragraphs 121 or 124 or otherwise suggest that the '085 publication expressly teaches treatment of these patients. In contrast, Petitioner's Reply now contends for the first time that the '085 publication itself teaches treatment of steroid-dependent/ refractory, steroid-resistant, and refractory patients by teaching sequential combination therapy with ibrutinib and steroids. Pet. Reply 9–10 (citing Ex. 1002 ¶¶ 121, 124).

There is some overlap between the arguments in the Petition and those in the Reply because, as discussed *infra,* Petitioner's new anticipation argument still relies on the knowledge of the POSA to infer administration to the relevant patient population. Nonetheless, the difference between Petitioner's arguments is significant and the timing of Petitioner's change in

theories leaves us with an incomplete record.[9] *See Ariosa Diagnostics v. Verinata Health, Inc.,* 805 F.3d 1359, 1376–68 (Fed. Cir. 2015) (finding that the Board did not err in declining to consider "previously unidentified portions of a prior art reference" where the petition "point[ed] to a generic statement in [the reference] that any sequencing method can be used" and petitioner did not identify "specific embodiments of [the reference]" that use a particular sequencing method until filing a reply).

Our rules require that a Petition must identify "[t]he supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge." 37 C.F.R. § 42.104(b)(5). Our rules also provide that we "may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge" in the Petition. *Id.*

The portion of the '085 publication cited by Petitioner in its Reply was not identified in the Petition. Pet. 38–39. Petitioner contends that it is entitled to rely on the previously uncited portions of the '085 publication because Patent Owner stated in its Response: "[i]t is undisputed that the steroid-resistant/refractory limitations are not disclosed in the '085 Publication." Mtn. Opp. 1 (citing PO Resp. 20). Petitioner argues that "[r]eplies are a vehicle for responding to arguments raised in a corresponding patent owner response." *Id.* at 2 (citing *Unified Patents v.*

[9] For example, the record does not include evidence from Patent Owner on the nature of the drugs recited in paragraph 124 of the '085 publication or on how the POSA would interpret the disclosure of sequential combination therapy in paragraph 121 of the '085 publication.

Intellectual Ventures, IPR2016-01643, Paper 51 at 50 (PTAB Mar. 26, 2018)). We are not persuaded.

While we agree that replies are a vehicle for responding to arguments, they are not a vehicle for introducing new theories of unpatentability. *See, e.g., Juniper Networks v. Chrimar Sys.*, IPR2016-01391, Paper 66 at 77 (PTAB Dec. 20, 2017) (cited by Petitioner at Mot. Opp. 2) ("Thus, the portions of Petitioner's Reply that address Bob Smith terminations and common mode chokes are a proper response to an argument raised by Patent Owner in the Response, not a new theory of unpatentability.").

Here, Petitioner's reliance on the '085 publication's disclosure of sequential combination therapy is a new theory of unpatentability, not a proper response to Patent Owner's argument. Indeed, it is difficult to characterize the statement that Petitioner purports to respond to as an argument at all. Rather, the statement at issue – "[i]t is undisputed that the steroid-resistant/refractory limitations are not disclosed in the '085 Publication" – is more aptly characterized as describing Petitioner's position than as setting forth an argument that justifies responsive evidence. While Petitioner is certainly entitled to correct mischaracterizations of its position, it is not entitled to advance a new theory of unpatentability simply to counter Patent Owner's statement that it was not advancing that theory. Accordingly, we exclude Petitioner's new argument from consideration.

Even if we were to consider Petitioner's new argument, we would not find it persuasive for two reasons. First, the '085 publication discloses a long list of drugs that can be used in combination with ibrutinib to treat auto-immune diseases (Ex. 1002 ¶ 124) and a long list of autoimmune diseases (*id.* ¶ 98). Arriving at the use of steroids in combination with ibrutinib to

treat patients with GVHD – the first analytical step in Petitioner's new anticipation theory – requires too much picking and choosing among therapies and diseases. *In re Arkley,* 455 F.2d 586, 587–588 (CCPA 1972) (In order for a reference to anticipate a claim, it must "clearly and unequivocally disclose the claimed [method] or direct those skilled in the art to the [product] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.").

Second, claims 4, 13, and 15 require treating steroid-dependent/refractory, steroid-resistant, or refractory cGVHD patients. Dr. Ferrara testifies that in such patients, ibrutinib is administered "when steroids are not effectively treating the GVHD." Ex. 1006 ¶ 86. The '085 publication states:

> The compounds of the present disclosure may be used in combination with one or more other drugs in the treatment of diseases or conditions for which compounds of the present disclosure or the other drugs may have utility, ***where the combination of the drugs together are safer or more effective than either drug alone***. Such other drug(s) may be administered . . . contemporaneously or sequentially with a compound of the present invention.

Ex. 1002 ¶ 121 (emphasis added). This disclosure is not the same as disclosing the use of ibruinib "when steroids are not effectively treating the GVHD," i.e, when the patient has steroid-dependent/refractory, steroid-resistant, or refractory cGVHD. Ex. 1006 ¶ 86. To arrive at the method of claims 4, 13, and 15 from the disclosure of combination therapy in the '085 publication, Petitioner must draw on the knowledge of the POSA to infer a specific patient population and to infer a sequence of administration in

which ibrutinib is administered after treatment with steroids.[10] This is not permissible. *Connell v. Sears, Roebuck & Co*., 722 F.2d 1542, 1548–49 (Fed. Cir. 1983) (rejecting argument that anticipation may be shown where the "general aspects" of a reference are the same as recited in a claim and "the differences in minor matters is only such as would suggest itself to one of ordinary skill in the art").

Accordingly, even if we were to consider Petitioner's new anticipation theory, we would find that Petitioner has not established, by a preponderance of the evidence, that the '085 publication anticipates claims 4, 13, and 15.

Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15. Because the preponderance of the evidence does not support that the '085 publication anticipates claims 4, 13, and 15, it necessarily also does not support that the '085 publication anticipates dependent claims 28–31, 43–46, and 50–53.

Claims 6–8

Claims 6–8 recite patient outcomes, including that the patient achieves a "partial response" (claim 6), that the patient achieves a "complete response" (claim 7), and that the "the severity of the GVHD is reduced" (claim 8).[11] Petitioner argues that the additional limitations in claims 6–8, recite patient outcomes that simply express the intended result of the recited method, and thus the additional limitations recited in these claims are not

[10] Manifestly, a patient must first have been administered steroids in order to have become steroid-dependent/refractory, steroid-resistant, or refractory.
[11] Claims 29–31, 44–46, and 51–53 each also recite one of these three possible outcomes. We do not discuss them here because they depend from claims 4, 13, and 15 and, as discussed above, we have determined that a preponderance of the evidence does support that the '085 publication anticipates claims 4, 13, and 15.

entitled to patentable weight. Pet. 40. In addition, Petitioner argues that even if these limitations are given patentable weight, the "patient outcomes recited in these dependent claims are an inherent and necessary effect of administering a therapeutically effective amount of ibrutinib to a patient with chronic GVHD." *Id.*; *see also,* Ex. 1006 ¶ 88.

Patent Owner contends that these limitations are "efficacy limitations" that must be given patentable weight. PO Resp. 5–16. Patent Owner also disputes Petitioner's contention that the efficacy limitations are inherent in the administration of a therapeutically effective amount of ibrutinib because some patients show no response, some patients achieve a partial response, and some patients achieve a complete response. *Id.* at 13.

We do not resolve the claim construction issue of whether these limitations should be given patentable weight because we find that even if the limitations recited in claims 6–8 were given patentable weight, they would have been inherent in the administration of a therapeutically effective amount of ibrutinib. We recognize that the administration of a therapeutically effective amount of ibrutinib will not, in all patients, result in any one of the three potential outcomes recited in claims 6–8. Ex. 2055 ¶ 142. However, on the facts of this case, the potential for different outcomes does not preclude a finding of anticipation, as reflected in our reviewing court's decision in *King Pharmaceuticals Inc., v. Eon Labs, Inc.,* 616 F.3d. 1267 (Fed. Cir. 2010).

The patent claim at issue in *King* was drawn to a "method of increasing the bioavailability of metaxalone" by administering "a therapeutically effective amount of metaxalone in a pharmaceutical composition with food." *Id.* at 1274. On appeal, patentee argued that

defendant had not established inherent anticipation because it had not provided any evidence or expert testimony that the prior art would *necessarily* result in an increase in metaxalone's bioavailability. *Id.* In contrast, patentee had provided expert testimony that "taking metaxalone with food would not inherently . . . increase[e] the bioavailability of metaxalone." *Id.* at 1275. Our reviewing court nevertheless found the challenged claim anticipated because "[a]s taught by the [challenged] patent, the only steps required to increase metaxalone's bioavailability [were] (1) ingesting metaxalone (2) with food" and because "[t]hese steps [were] undeniably disclosed by the prior art." *Id.* at 1276. The court explained:

> To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does. *See Hewlett–Packard Co. v. Mustek Systems, Inc.,* 340 F.3d 1314, 1326 (Fed. Cir. 2003) ("[A] prior art product that sometimes, but not always, embodies a claimed method nonetheless teaches that aspect of the invention."). Because the [challenged] patent discloses no more than taking metaxalone with food, to the extent such a method increases the bioavailability of metaxalone, the identical prior art method does as well. As the district court aptly stated, "to inherently anticipate, the prior art need only give the same results as the patent, not better." *King Pharms., Inc.,* 593 F.Supp.2d at 509.

Id.

Here the only step required to achieve the claimed patient outcome is to administer a therapeutically effective amount of ibrutinib. As discussed above, the '085 publication discloses performing this same method step. Patent Owner does not identify, and we do not find, that the '865 patent identifies any different or additional steps that must be performed in order to obtain a particular one of the three recited outcomes. That performing the step of administering ibrutinib may achieve the claimed patient outcomes in

some patients but not in others does not prevent a finding of anticipation because, under *King,* "the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *Id.* Because there are no differences between the claimed step and the step disclosed in the prior art, we find that the '085 publication inherently discloses the patient outcomes recited in claims 6–8.

Claim 10[12]

Claim 10 depends from claim 1 and further requires that "the patient had a hematopoietic cell transplantation." Ex. 1001, 76:42–32. Petitioner presents the testimony of Dr. Ferrara that "GVHD is a potentially serious complication of allogeneic hematopoietic stem cell transplantation, which is commonly known as bone marrow transplantation." Ex. 1006 ¶ 24. Thus, according to Petitioner, having a hematopoietic cell transplantation is a "prerequisite" to developing GVHD. Pet. 42. Patent Owner does not separately argue the patentability of claim 10. *See generally,* PO Resp.[13]

[12] We address claim 10 before addressing claim 9 because our discussion of the evidence with respect to claim 9 builds on our discussion of the evidence with respect to claim 10.

[13] In its Preliminary Response, Patent Owner argued that Petitioner improperly relied on the knowledge of the POSA to supply the missing element of treating patients having received a hematopoietic cell transplantation. Prelim. Resp. 38. This argument is waived because Patent Owner did not pursue it in its post-institution briefing. *See* Paper 9, 7 ("Patent Owner is cautioned that any arguments for patentability not raised in the response may be deemed waived.") Even if we were to consider this argument, we would find it unpersuasive for the reasons set forth in our Institution Decision. Inst. Dec. 21–22.

We agree with Petitioner that the '085 publication anticipates claim 10. The evidence of record supports that cGVHD is a complication of allogeneic hematopoietic stem cell transplantation and that "virtually all chronic GVHD patients have had a hematopoietic cell transplantation." *See* Ex. 1006 ¶¶ 24, 94. For this reason, we agree with Petitioner that the POSA would have immediately understood the disclosure of the '085 publication of treating patients with GVHD to refer to treating patients who had received a hematopoietic cell transplant and developed GVHD as a complication of that transplant. Accordingly, the preponderance of the evidence supports that the '085 publication anticipates claim 10.

Claim 9

Claim 9 depends from claim 1 and further requires that "the patient ha[ve] chronic lymphocytic leukemia (CLL)." Ex. 1001, 76:40–41. Dr. Ferrara testifies that "hematopoietic stem cell transplantation [discussed above in connection with claim 10] is used to treat approximately a dozen diseases" including, chronic lymphocytic leukemia. Ex. 1006 ¶ 26.

Petitioner contends that the '085 publication anticipates claim 9 because it discloses the use of ibrutinib to treat chronic lymphocytic leukemia. Pet. 41 (citing Ex. 1002 ¶¶ 4, 5, 97); Ex. 1006 ¶ 90 (discussing same). Thus, according to Petitioner, "upon reading the '085 Publication's disclosure, a POSA would have at once envisaged that in order to develop chronic GVHD the patient had one of approximately a dozen diseases, including CLL." Pet. 41–42 (citing Ex. 1002 ¶¶ 90–92). Patent Owner does

not argue the patentability of claim 9 based on the patient having CLL. *See generally,* PO Resp.[14]

We agree with Petitioner that the '085 publication anticipates claim 9. In order to anticipate claim 9, the '085 publication must disclose treatment of a patient with CLL and with cGVHD. The '085 publication discloses treatment both of CLL and of GVHD; however, these two diseases are disclosed as two among many diseases that may be treated using ibrutinib. *See, e.g.*, Ex. 1002 ¶¶ 96–101. Accordingly, anticipation turns on "'whether the number of categories and components' disclosed in [the '085 publication] is so large that the combination of [treating a patient with both CLL and cGVHD] 'would not be immediately apparent to one of ordinary skill in the art.'" *Kennametal*, 780 F.3d at 1382. The evidence of record supports that given the medical connection between CLL and cGVHD (*see* Ex. 1006 ¶ 92), it would have been immediately apparent to the POSA to treat a patient having both CLL and cGVHD. Accordingly, the preponderance of the evidence supports that the '085 publication anticipates claim 10.

[14] In its Preliminary Response, Patent Owner argued that Petitioner improperly relied on the knowledge of the POSA to supply the missing element of treating patients having CLL. Prelim. Resp. 38. This argument is waived because Patent Owner did not pursue it in its post-institution briefing. *See* Paper 9, 7 ("Patent Owner is cautioned that any arguments for patentability not raised in the response may be deemed waived.") Even if we were to consider this argument, we would find it unpersuasive for the reasons set forth in our Institution Decision. Inst. Dec. 22–23.

Claims 24, 35, 39, and 55

Dependent claims 24, 35, and 39 recite administering "about 420 mg of [ibrutinib] . . . orally once per day."[15] Independent claim 55 recites "administering . . . about 420 mg/day of [ibrutinib]." Petitioner contends that the '085 publication "repeatedly discloses administering ibrutinib to a patient in an oral dosage of 420 mg/day." Pet. 43 (citing Ex. 1002 ¶¶ 30, 120). According to Petitioner, the '085 publication "discloses use of ibrutinib at 420 mg/day in Phase II clinical trials [for treatment of chronic lymphocytic leukemia], meaning ibrutinib had already been used safely at that dosage in earlier, Phase I safety trials." *Id.* at 44 (citing Ex. 1002 ¶¶ 4, 5 and Ex. 1006 ¶¶ 96–101). Petitioner also contends that the '085 publication discloses that "ibrutinib can be administered orally once per day" and "can be administered in single or multiple doses" per day. *Id.* (citing Ex. 1002 ¶¶ 30, 93, 94, 120, and claim 20).

Patent Owner argues that the '085 publication "lists a huge number of diseases and a wide variety of potential doses, explaining that the dose will vary depending on the disease and its severity, and the age, weight, and other characteristics of the mammal to be treated." PO Resp. 51. Patent Owner further argues that "Petitioner makes no showing as to why a POSA would have selected, from the thousands of potential embodiments in the '085 Publication, the particular claimed dose, administration regimen,

[15] Claims 28, 43, and 50, each also recite administering "about 420 mg of [ibrutinib] . . . orally once per day." We do not discuss them here because they depend from claims 4, 13, and 15 and, as discussed above, we have determined that a preponderance of the evidence does support that the '085 publication anticipates claims 4, 13, and 15.

disease, and patient subpopulations, with a reasonable expectation of therapeutic efficacy." *Id.*[16]

For the reasons discussed in connection with claim 1, we find that the POSA would reasonably have connected the disclosure in the '085 publication that in an "eighth aspect of the present disclosure" ibrutinib can be used to treat GVHD with the dosages of ibrutinib provided in elsewhere in the disclosure. *See supra* p. 14–17. The dosages disclosed in the '085 publication include a dose of 425 mg and ranges encompassing the claimed 420 mg/day. Ex. 1002 ¶¶ 30, 120. Moreover, Patent Owner has not argued or identified evidence to support that the claimed dosing of 420 mg/day is critical (*see generally,* PO Resp. 50–52) and, in fact, the '604 patent identifies doses ranging from 40 mg/day to 840 mg/day as "therapeutically effective" (Ex. 1001, 76:7–10 (claim 5)). While we recognize the potential that a particular dose may be critical, in the absence of supporting evidence, we will not speculate as to whether the claimed dose meets the criteria for establishing criticality. Accordingly, we find that the '085 publication anticipates claims 24, 35, 39, and 55. Ex. 1002 ¶¶ 30, 120. *See ClearValue, Inc. v. Pearl River Polymers, Inc.,* 668 F.3d 1340, 1345 (Fed. Cir. 2012) (finding that disclosure of a range of raw alkalinity of less than 150 ppm anticipated a claim requiring 50 ppm where there was "no allegation of criticality or any evidence demonstrating any difference across the range").

[16] On the cited pages, Patent Owner also makes arguments relating to obviousness for these claims. We do not address these argument here as this discussion is focused on anticipation.

III. GROUND 2: OBVIOUSNESS OVER THE '085 PUBLICATION

Petitioner asserts that the '085 publication renders claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent obvious. Pet. 44–53. We limit our discussion to whether the '085 publication would have rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious because we have already determined that a preponderance of the evidence supports that the '085 publication anticipates claims 1, 6–10, 24, 35, 39, and 55. We have reviewed Petitioner's and Patent Owner's assertions, as well as the evidence of record, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 4, 13, 15, 28–31, 43–46 and 50–53 would have been obvious over the '085 publication.

A. Factual Background

The evidence supports that a POSA would have viewed cGVHD as a "complex and poorly understood" disease. Ex. 2059, abstract; Ex. 2003, 80 ("the biology of CGVHD has not been determined"); *id.* at 81 ("the pathophysiology of CGVHD, unlike that of acute GVHD, remains obscure"); Ex. 2006 ("Chronic GVHD was recognized as a complication of allogeneic hematopoietic cell transplantation more than 30 years ago, but progress has been slowed by the limited insight into the pathogenesis of the disease and the mechanisms that lead to development of immunological tolerance."); Ex. 2054, 2 (article coauthored by Dr. Ferrara noting a "lack of significant understanding of the immunobiology of chronic GVHD when compared with acute GVHD"); Ex. 2007, 1556 (article coauthored by Dr. Ferrara stating "[b]y contrast with acute GVHD, the pathophysiology of chronic GVHD remains poorly understood"); Ex. 2059, 204 ("cGVHD is a

multiorgan alloimmune and autoimmune disorder characterized by immune dysregulation, immune deficiency, impaired end-organ function and decreased survival. Although these features of cGVHD were noted > 30 years ago there has been little progress sorting out the precise mechanism(s).").

The POSA would have attributed the lack of understanding of cGVHD in part to the absence of predictive models and standardized criteria for measurement. Ex. 2003, 80 (teaching that "defining the pathophysiology of CGVHD has been complicated by the absence of animal models that accurately recapitulate the disease or its clinical setting"); Ex. 2054, 2 (article coauthored by Dr. Ferrara stating that the "paucity of appropriate mouse models for chronic GVHD has resulted in a lack of significant understanding of the immunobiology of chronic GVHD when compared with acute GVHD"); Ex. 2056, 73–74 (Dr. Ferrara's testimony agreeing that "the lack of standardized criteria for quantitative measurement of therapeutic response in clinical trials poses a major obstacle for the development of new agents in chronic Graft-versus-host disease"); Ex. 2048, abstract ("The lack of standardized criteria for quantitative measurement of therapeutic response in clinical trials poses a major obstacle for the development of new agents in chronic graft-versus-host disease.").

Not surprisingly, given the poor understanding of the disease, the evidence supports that the POSA would have understood that treating patients with cGVHD was very difficult. Ex. 2045, 2 (article by Dr. Ferrara teaching that treating patients with advanced cGVHD "is one of the most challenging scenarios, not only in transplant medicine, but in all of medicine"). As Dr. Ferrara explained in his deposition, cGVHD patients are

"often on 15 or 20 medications a day" and, as a result, treating them is "has now become a sort of three-dimensional chess game as opposed to the largely two-dimensional chess game that acute Graft-versus-host disease treatment is, because you've got a much firmer baseline . . . [and] better animal models." Ex. 2056, 92:9–15.

More importantly for purposes of obviousness, the evidence supports that a POSA would have viewed treating patients with cGVHD as highly unpredictable and relied on trial and error to identify drugs for treating individual patients. Ex. 2007, 1556 (article coauthored by Dr. Ferrara stating "[t]he response of chronic GVHD to treatment is unpredictable, and mixed responses in different organs can take place in the same patient"); Ex. 2050, 2 ("Although different treatment options are available for salvage therapy of steroid refractory cGVHD, the 'trial-and error system' remains to date the only way to identify the drug or drug combination effective in an individual patient."); Ex. 2059, 207 ("cGVHD is complex and there are no convincing surrogate *in-vitro* or *in-vivo* parameters to predict benefit.").

A POSA would have viewed steroid-dependent/refractory, steroid-resistant, and refractory patients as particularly difficult to treat. Ex. 2055 ¶ 38 (Dr. Koreth's well supported testimony summarizing the prior art as recognizing that "steroid-dependent/refractory, steroid-resistant, or refractory cGVHD patients were very hard to treat."); *id.* ¶¶ 35–37 (discussing unsuccessful attempts to treat such patients); *id.* ¶¶ 174–180 (discussing safety concerns for drugs, like ibrutinib, that target B and T cells when administered to steroid-dependent/ refractory, steroid-resistant, or refractory cGVHD patients); Ex. 2056, 124:7–11 (Dr. Ferrara testimony: "[A] patient with chronic GvHD, particularly one who is being treated for

chronic GvHD [i.e. treated with steroids], has an immune system that is less than that of a newborn baby. Less effective or less protective than that of a newborn baby."); Ex. 2059, 207 (stating that "[t]here are major challenges to developing therapy for cortico-steroid-resistant cGVHD" and identifying some of these challenges).

Given the poor understanding of cGVHD, the lack of animal models and standardized measurement criteria, and the unpredictability in the field, it is not surprising that many potential treatments have proven unsuccessful. Ex. 2045, 2 (article by Dr. Ferrara stating "[d]espite dozens of trials, nothing has ever worked, in part because we have not had good drugs, and in part because the trials are difficult to perform."); Ex. 2055 ¶ 147 (Dr. Koreth testimony regarding the "litany of treatment failures for cGVHD patients known in the art"); *id.* ¶¶ 43–51, 221–225 (discussing specific failed treatments for cGVHD); Ex. 2046, 1 (article reporting that "very smart senior VP of a pharma company" told Dr. Ferrara that "GVHD is where new drugs go to die"); Ex. 2059, 203 ("There has been little progress over the past 30 years in preventing and/or treating cGVHD."); *id.* at 204–205 (teaching that "[t]here is no standard next therapy" after treatment with steroids and noting that "recommended interventions include about 40 drugs, all studied in poorly standardized, phase-2 trials or reported in retrospective case analyses"); Ex. 2056, 222:13–223:13 (Dr. Ferrara testimony explaining that "between 20 and 30 compounds" have been tested for treatment of cGVHD and "even more compounds have been tried but not reported on"). In view of these failures, the POSA would have viewed potential new treatments with some degree of skepticism. *See e.g.,* Ex. 2006, 158 ("The contrast with results of the prospective phase III trial testing MMF for initial

treatment of chronic GVHD raises a general concern that other previously tested agents also do not provide as much benefit [for treating cGVHD] as suggested in the reports.")

We view Petitioner's evidence and argument as to why the POSA would reasonably have expected to be able to treat the patient populations identified in claims 4, 13, and 15 against the above discussed factual backdrop.

B. Disclosures of the Asserted Prior Art

The '085 Publication

The disclosure of the '085 publication is discussed *supra* p. 9–10.

C. Analysis

Claims 4, 13, and 15 depend from claim 1 and provide additional limitations concerning the patient to whom ibrutinib is administered. Claim 4 specifies that "the patient has steroid-dependent/refractory chronic GVHD." Claim 13 specifies that "the chronic GVHD is steroid resistant GVHD." And claim 15 specifies that "the chronic GVHD is refractory GVHD." Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15.

Petitioner, supported by Dr. Ferrara, contends that "a POSA would have known, and it would have been obvious, that additional treatments for chronic GVHD, including specifically administering ibrutinib, would have been employed where steroid treatment was not effective for treating chronic GVHD." Pet. 49; *see also* Ex. 1006 ¶ 108 (Dr. Ferrara testifying that "it would have been obvious to a POSA that administering ibrutinib to a patient

with chronic GVHD would be warranted in situations where treatment beyond steroids was necessary because either the chronic GVHD was getting worse after the steroids had been removed (as in claim 4) or the steroids had not worked to treat the chronic GVHD (as in claims 4, 13, and 15).").

Patent Owner argues, *inter alia,* that Petitioner has not met its burden to establish that a POSA would reasonably have expected ibrutinib to successfully treat steroid-resistant, steroid-dependent and refractory patients. PO Resp. 24–28. Patent Owner points out that "steroid-resistant/refractory patients were especially difficult to treat since prior steroid administration results in an immunocompromised, heterogeneous, and vulnerable patient population." *Id.* at 27. Patent Owner argues that the '085 publication lacks data showing that ibrutinib can be used to treat cGVHD and that a POSA "would have read this deficient disclosure against the litany of failures for treating steroid-resistant and refractory patients." *Id.* at 26, 27. We agree with Patent Owner that the record does not support that the POSA would reasonably have expected, based on the '085 publication, that ibrutinib could be used to successfully treat steroid-resistant, steroid-dependent and refractory cGVHD patients.

Petitioner's position on why the POSA would have expected success in administering ibrutinib to cGVHD patients in the claimed patient populations appears be, essentially, that the POSA would have expected administration of ibrutinib to be successful because the '085 publication teaches to administer ibrutinib to treat chronic GVHD. Pet. 48 ("In fact, as explained by Dr. Ferrara, a POSA would have understood the disclosure of 'graph versus host disease' in the '085 Publication to concern ***chronic***

GVHD in particular. Accordingly, a POSA would have reasonably expected that administering ibrutinib to patients with chronic GVHD would successfully treat the disease, rendering claim 1 obvious.") (internal citation omitted); *id.* at 49 ("A POSA would have known, and it would have been obvious, that additional treatments for chronic GVHD, including specifically administering ibrutinib, would have been employed where steroid treatment was not effective for treating GVHD."); *see also,* Ex. 1006 ¶¶ 106–108 (Dr. Ferrara testimony to the same effect). We do not find this persuasive.

In the absence of data showing ibrutinib to be effective in treating steroid-dependent/refractory, steroid-resistant, and/or refractory cGVHD patients, we do not find the bald teaching that ibrutinib can be used to treat the genus GVHD to be sufficient to provide the POSA with a reasonable expectation of success. Simply put, the factual background described above – reflecting a poor understanding of cGVHD, an absence of predictive models and standardized measurement criteria, a multitude of unsuccessful treatments, unpredictability with respect to treatments, and trial and error testing – outweighs the unsupported teaching of the '085 publication, particularly when applied to the difficult-to-treat patient subpopulations recited in claims 4, 13, and 15; *see* Ex. 1030, 149:14–150:7 (Dr. Koreth testimony that POSA would expect cGVHD treatments to fail). We find that even considering the disclosure in the '085 publication that ibrutinib can be used to treat the genus GVHD, the POSA would not reasonably have expected success in doing so with respect to the patient subpopulations recited in claims 4, 13, and 15.

Accordingly, we find that Petitioner has not established, by a preponderance of the evidence, that claims 4, 13, and 15 would have been

obvious in view of the '085 publication.[17] Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15. Because the preponderance of the evidence does not support that the '085 publication renders claims 4, 13, and 15 obvious, it necessarily also does not support that the '085 publication renders dependent claims 28–31, 43–46, and 50–53 obvious.

IV. GROUND 3: OBVIOUSNESS OVER THE COMBINATION OF THE '085 PUBLICATION, SHIMABUKURO-VORNHAGEN, AND HERMAN

Petitioner asserts that the combination of the '085 publication, Shimabukuro-Vornhagen, and Herman renders claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent obvious. Pet. 54–62. We limit our discussion to whether the '085 publication, Shimabukuro-Vornhagen, and Herman would have rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious because we have already determined that a preponderance of the evidence supports that the '085 publication anticipates claims 1, 6–10, 24, 35, 39, and 55. We have reviewed Petitioner's and Patent Owner's assertions, as well as the evidence of record, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 4, 13, 15, 28–31, 43–46 and 50–53 would have been obvious over the combination of the '085 publication, Shimabukuro-Vornhagen, and Herman.

[17] Patent Owner included extensive discussion of objective indicia of non-obviousness. PO Resp. 57–65. We have determined that it is not necessary to address this evidence in detail because it can only benefit the Patent Owner and we have already determined that the evidence does not support a finding that claims 4, 13, 15, 28–31, 43–46, and 50–53 would have been obvious over the '085 publication.

The factual background discussed above with respect to Ground 2 (*see supra* p. 35–39.) applies equally with respect to Ground 3. The following additional considerations apply to our discussion of ground 3.

A. Disclosures of the Asserted Prior Art

The ’085 Publication

The disclosure of the ’085 publication is discussed *supra* p. 9–10. In addition to the disclosures of the ’085 publication already discussed, the ’085 publication also discloses that “[i]brutinib is an orally available drug that targets Bruton’s tyrosine kinase (BTK)” and serves as an “irreversible small molecule BTK inhibitor.” Ex. 1002 ¶ 4. The ’085 publication further discloses that the “development of drugs which inhibit BTK can have therapeutic significance in the treatment of both B cell-related hematological cancers . . . and autoimmune diseases.” *Id.* ¶ 2.

Shimabukuro-Vornhagen

Shimabukuro-Vornhagen discloses that “[s]everal independent lines of evidence clearly demonstrate that B cells are involved in the pathogenesis of chronic GVHD.” Ex. 1003, 4922. The reference also discloses that “[t]he incidental clinical observation that treatment of immune thrombocytopenia in a patient with chronic GVHD with rituximab led to improvement of some manifestations of chronic GVHD . . . raised the question whether the depletion of B cells could be used to treat chronic GVHD.” *Id.* at 4923. Shimabukuro-Vornhagen concludes that “B-cell depletion may . . . be a promising approach for the treatment of chronic GVHD.” *Id.*

Herman

Herman discloses that ibrutinib “promotes apoptosis, inhibits proliferation, and also prevents CLL cells from responding to survival

stimuli provided by the microenvironment." Ex. 1004, 6288. Herman concludes that "these studies provide significant support for the development of [ibrutinib] as a therapeutic agent for the treatment of CLL and related diseases." *Id.* Herman also discloses that ibrutinib "can inhibit production of inflammatory cytokines such as IL-6, IL-10, and TNF-α." *Id.* at 6291.

D. Analysis

As discussed above, claims 4, 13, and 15 depend from claim 1 and provide additional limitations concerning the patient to whom ibrutinib is administered. Claim 4 specifies that "the patient has steroid-dependent/ refractory chronic GVHD." Claim 13 specifies that "the chronic GVHD is steroid resistant GVHD." And claim 15 specifies that "the chronic GVHD is refractory GVHD." Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15.

Petitioner argues that "[t]he '085 publication teaches administering ibrutinib to treat a number of conditions in which B cells play a key role, including 'graft versus host disease.'" Pet. 55. According to Petitioner, the '085 publication teaches that ibrutinib targets Bruton's tyrosine kinase (BTK), an enzyme in B cells, "thus preventing B cells from activating downstream T cells." *Id.* Petitioner also argues that Shimabukuro-Vornhagen teaches that "B cells are involved in the pathogenesis of chronic GVHD" and that drugs that "inhibited or depleted (i.e. killed) B cells and prevented their activation of downstream T cells successfully treated chronic GVHD." *Id.* As to the expectation of success, Petitioner concludes: "considering that ibrutinib was a known BTK inhibitor (i.e. a drug that works on B cells) in light of Shimabukuro-Vornhagen's disclosures that B-

cell inhibiting drugs treat chronic GVHD, a POSA would have reasonably expected that ibrutinib would treat chronic GVHD." *Id.* at 58.

Petitioner also argues that it was "well known that inflammatory cytokines are produced in an abnormal fashion in patients with chronic GVHD." *Id.* at 57 (citing Ex. 1010, 169 (disclosing that "[c]ytokines play a key role in pathogenesis of chronic Graft versus Host Disease (cGVHD) and various studies have shown abberant [sic] production of cytokines by immune cells from GVHD patients.")). Petitioner contends that Herman provides additional motivation to use ibrutinib to treat chronic GVHD by teaching that "ibrutinib inhibits the production of [the] same inflammatory cytokines that were known to contribute to the cause of chronic GVHD." *Id.* (citing Ex. 1006 ¶ 125). Petitioner contends that the knowledge that ibrutinib inhibits inflammatory cytokines would provide an "additional reason" why "a POSA would have had a reasonable expectation of success in using ibrutinib to treat chronic GVHD." *Id.* at 58–59.

Patent Owner argues, *inter alia,* that a POSA would not reasonably have expected success in treating the recited patient population in view of the combined disclosures of the '085 publication, Shimabukuro-Vornhagen, and Herman. PO Resp. 31–43. With respect to Shimabukuro-Vornhagen, Patent Owner contends that a POSA, aware of all of the pertinent art, would have been skeptical of Shimabukuro-Vornhagen's "small, uncontrolled, non-standardized" study. PO Sur-reply 19. Patent Owner also argues that Shimabukuro-Vornhagen's teachings are based on rituximab, a drug that "target[s] *different* molecules, expressed in *different* cells, that exert[s its] influence through [a] *different* molecular pathway[], and ha[s] *different* effects on B cells" than ibrutinib." *Id.*

With respect to Herman, Patent Owner contends that Petitioner ignores: "(1) ibrutinib's reported inhibition of IL-10, which multiple references (including those from Petitioner's expert) characterized as a *beneficial* anti-inflammatory cytokine that could be used to *prevent* GVHD; (2) the uncertain relationship between cytokine levels and cGVHD; and (3) the understanding that many drugs targeting TNFα or IL-6R were *not* recommended for treating cGVHD." *Id.* at 19–20. We agree with Patent Owner that the evidence of record does not support a reasonable expectation of success.

Our analysis first considers the contribution of Shimabukuro-Vornhagen to a reasonable expectation of success. More particularly, it considers Shimabukuro-Vornhagen's teaching, based on rituximab, that B–cell depletion may be a promising approach for treating cGVHD, and it considers whether the POSA would expect that teaching to carry over to ibrutinib. It also considers the import of Shimabukuro-Vornhagen's teaching that B cells are involved in the pathogenesis of cGVHD. After evaluating the contribution of Shimabukuro-Vornhagen, our analysis considers the contribution of Herman and whether the knowledge that ibrutinib inhibits the cytokines IL-6, IL-10, and TNF-α contributes to a reasonable expectation of success. We then consider the teaching of the '085 publication that ibrutinib can be used to treat GVHD and, more generally that BTK inhibitors can be used to treat autoimmune diseases. Finally, we consider all of the evidence together and reach a conclusion as to whether the cited art supports that the POSA would reasonably have expected success in treating cGVHD patients having steroid-dependent/refractory, steroid- resistant and/or refractory cGVHD using

ibrutinib. We conclude that the cited art does not support a reasonable expectation of success.

1. Contribution of Shimabukuro-Vornhagen to a reasonable expectation of success

Shimabukuro-Vornhagen states that "B-cell depletion may . . . be a promising approach for the treatment of chronic GVHD, particularly steroid refractory skin disease." Ex. 1003, 4923. As discussed above, in the absence of data showing a drug to be effective in treating steroid-dependent/ refractory, steroid-resistant, and/or refractory cGVHD patients, a POSA would not find a bald teaching that a drug can be used to treat cGVHD to be sufficient to provide a reasonable expectation of success. *See supra* p. 35–42. Patent Owner argues that Shimabukuro-Vornhagen lacks *in vitro,* preclinical, or clinical data. PO Resp. 30–31. Shimabukuro-Vornhagen, however, is not completely devoid of supporting data.

Shimabukuro-Vornhagen's statement that B-cell depletion may be a "promising approach" is a conclusion drawn largely from analysis of eight "case series and small clinical trials" studying the effectiveness of rituximab. Ex. 1003, 4923. Shimabukuro-Vornhagen's statement that targeting B cells with rituximab was "promising" thus has some evidentiary grounding. Nonetheless, Shimabukuro-Vornhagen recognized the limitations of its data, concluding that "[f]ormal proof in the form of a prospective, randomized clinical trial with long-term follow up will still be required." *Id.* at 4924.

Shimabukuro-Vornhagen's conclusions are largely consistent with a meta-analysis, cited by Patent Owner (PO Resp. 39–40), analyzing much the same studies that Shimabukuro-Vornhagen analyzed.[18] The meta-analysis

[18] Shimabukuro-Vornhagen analyzed eight rituximab studies. Ex. 1003, 4923 (see particularly Table 1, listing studies). The meta-analysis analyzes

found that the studies "suggest that rituximab is effective in treating cutaneous cGVHD" and noted that "steroid-refractory cGVHD demonstrates that the skin is the most responsive organ." Ex. 2052, 1009. Nonetheless, the meta-analysis found that the studies had several significant limitations, including the "absence of randomized trials," a "very small number of patients," "poor methodological quality," and "lack of a homogeneous response criteria among studies." *Id.* at 1011. The meta-analysis concluded "[i]t is important to understand that the totality of the evidence generated through this systemic review demonstrates the gaps in the existing evidence base related to the efficacy of rituximab in treating patients with steroid-refractory cGVHD." *Id.* at 1012. Thus looking at Shimabukuro-Vornhagen alone, or at Shimabukuro-Vornhagen together with the meta-analysis, the statement that "B cell depletion may . . . be a promising approach" provides some support for the proposition that a POSA would expect that rituximab might work for treating cGVHD patients, particularly those with steroid refractory skin disease.

The art, however, is not limited to just Shimabukuro-Vornhagen and the meta-analysis. In particular, the art includes George, a prior-art study conducted subsequent to Shimabukuro-Vornhagen, in which the authors "retrospectively reviewed the medical records of patients with steroid-refractory cutaneous cGVHD" who had been "treated with rituximab 375 mg/m^2 weekly for three to four doses." Ex. 2053, 737. The authors identified nine patients with steroid-refractory cutaneous cGVHD. *Id.* The authors noted that the above discussed meta-analysis had suggested that

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seven of these studies, omitting to consider a seven-patient study by Teshima et al. Ex. 2052, 1009.

rituximab might be effective in treating such patients, but found that "[n]one of our patients achieved a complete or partial response." *Id; see also* Ex. 2056, 146:2–147:23 (Dr. Ferrara testimony confirming same). This result diminishes the modest expectation created by the data reported in Shimabukuro-Vornhagen that rituximab would be effective in treating cGVHD in the claimed patient sub-populations.

We turn now to whether the POSA would have reasonably have expected Shimabukuro-Vornhagen's teachings with respect to the use of rituximab to translate to ibrutinib.

Rituximab is a "genetically engineered chimeric murine/human monoclonal antibody." Ex 2061, 1. Ibrutinib, in contrast, is a "small molecule inhibitor of BTK." Ex. 2036, 27. The two molecules also have different mechanisms of action. Rituximab binds to an antigen on the surface of B cells, causing their "rapid and selective *depletion."* Ex. 2055 ¶ 170. Ibrutinib "was understood *not* to deplete B cells and to bind an entirely different target [BTK] located within the cytoplasm of B cells," this "inhibit[s] activation of B cells, thereby arresting B cells in an unstimulated state." *Id.* ¶ 171. "Ibrutinib also directly targets T cells by covalently binding to ITK, a kinase in the T cell signaling pathway." *Id.* ¶ 172. "[U]nlike rituximab's target (CD20), ibrutinib's targets (BTK and ITK) are also expressed in many other cell types, including T cells, monocytes, macrophages, and mast cells." *Id.*

Dr. Koreth opines that these difference "matter in a clinical context" as evidenced by ability of ibrutinib to treat a patient for cGVHD after rituximab had failed. *Id.* ¶ 173. Dr. Ferrara acknowledges differences between the two drugs (Ex. 2056, 131:6–132:23 (Dr. Ferrara deposition

testimony)),[19] but finds a reasonable expectation of success based on the fact that both drugs prevent the activation of downstream T cells that mediate chronic GVHD (Ex. 1006 ¶ 128). We credit Dr. Koreth's well-supported, detailed, and specific testimony (Ex. 2055 ¶¶ 168–173) over Dr. Ferrara's more generalized, bird's-eye view testimony (Ex. 1006 ¶ 128). We find that the differences between ibrutinib and rituximab would have left the POSA with some reservations as to whether the two drugs would be similarly efficacious in treating an unpredictable disease like cGVHD, particularly as relates to the claimed patient populations.

Having considered Shimabukuro-Vornhagen's rituximab based teachings, we now consider its teaching that "several independent lines of evidence clearly demonstrate that B cells are involved in the pathogenesis of chronic GVHD." Ex. 1003, 4922. Petitioner relies on the knowledge that B cells are involved in cGVHD as support for its obviousness position. Pet. 55, 58. Patent Owner contends "the role of B cells in cGVHD pathogenesis was complex and poorly understood." PO Resp. 31 (emphasis omitted).

The evidence supports that a POSA would have known that B cells are involved in the pathogenesis of cGVHD. Ex. 1003 at 4922 ("Several independent lines of evidence clearly demonstrate that B cells are involved in the pathogenesis of chronic GVHD."); Ex. 2055 ¶ 26 (Dr. Koreth's testimony that the prior art reports that "T cells and B cells appear to be involved in cGVHD pathogenesis"). However, the evidence is inconclusive as to how B cells are "involved." Shimabukuro-Vornhagen itself teaches

[19] Dr. Ferrara also testified in his deposition that he did not know whether ibrutinib was known, as of October 2013, to inhibit ITK. Ex. 2055, 171:21–172:3.

that it was not clear whether B-cells were causing cGVHD or merely a marker of the disease. *Id.* at 4922–23 ("Whether the occurrence of antibodies in GVHD represents a bystander effect caused by polyclonal B-cell activation remains unknown. In fact, to date a direct involvement of autoantibodies in GVHD pathology has not been conclusively demonstrated."); *id.* at 4923 (teaching that "no direct evidence for the causal relationship of autoantibodies or alloantibodies and the pathogenesis of organ manifestations of chronic GVHD in humans exist."); *id.* at 4919 ("The mechanisms by which B cells contribute to acute and chronic GVHD currently are only incompletely understood."); Ex. 2055 ¶ 163 (Dr. Koreth testimony: "[T]he mechanisms by which B cells interact with T cells, and the resulting effect (if any) on cGVHD pathogenesis, were complex and far from understood in 2013."). Accordingly, the record supports, at best, a weak expectation that drugs that target B cells would be effective in treating the claimed patient populations based on mechanism of action.

Petitioner cites to several statements by Dr. Koreth to counter the evidence that the role of B cells was "only incompletely understood." Pet. Reply 19. For example, Petitioner cites Dr. Koreth's statement that "T cells and B cells appear to be involved in cGVHD pathogenesis" and his deposition testimony that there was "there was a growing sense that B-cells deserved looking at and may indeed . . . have a role to play in the pathogenesis or the development of chronic GVHD." *Id.* (citing Ex. 2055 ¶ 26 and Ex. 1030, 59:17–60:5). However these statements are consistent with and cumulative of what is taught in Shimabukuro-Vornhagen, particularly as Dr. Koreth does not indicate in his deposition that

the role B cells play in the pathogenesis of cGVHD was causative or even that the specific role was known.

Petitioner also cites Dr. Koreth's testimony that "'cGVHD clinical trial candidates targeted B cells' before 2013." *Id.* (citing Ex. 2055 ¶ 46 and Ex. 1030, 58:13–20). However, Dr. Koreth subsequently explains that these trials did not result in successful treatments, diminishing the import of the teaching that "clinical trial candidates targeted B cells." Ex. 2055 ¶¶ 46–47. Patent Owner cites several examples of drugs that were known to deplete B and T cells and that do not provide effective treatments for cGVHD, including include alemtuzumab, MMF, and azathioprine. PO Resp. 37 (citing evidence including e.g, Ex. 2050, Table 4, 9 (addressing alemtuzumab); Ex. 2019, abstract (addressing MMF); Ex. 2057, abstract (addressing azathioprine); and Ex. 2064, 1617 (also addressing azathioprine)); *see also,* Ex. 2055 ¶ 175–179 (Dr. Koreth's testimony discussing these drugs); Ex. 2015, 2657, 2661 (teaching that ABX-CBL, a monoclonal antibody that depletes T cells and B cells, demonstrated "no clinically or statistically significant advantage in regard to treatment response using ABX-CBL compared with ATG [antithyomocyte globulin], and survival was sufficiently unfavorable on ABX-CBL that one can rule out even moderate improvement relative to ATG."). Awareness of these unsuccessful treatments would, to some extent, have diminished the weak expectation that because B cells were known to be involved in the pathogenesis of cGVHD, drugs that target B cells could be used to successfully treat steroid-dependent/refractory, steroid-resistant, and refractory cGVHD patients.

2. Contribution of Herman to a reasonable expectation of success

Herman discloses that ibrutinib "can inhibit production of inflammatory cytokines such as IL-6, IL-10, and TNF-α." Ex. 1004, 6291. Petitioner contends that this teaching contributes to a reasonable expectation of success because it was well known the production of inflammatory cytokines contributes to the causing cGVHD. Pet. 56–57. We find that the teachings of Herman do not meaningfully contribute to an expectation that ibrutinib could be used to successfully treat patients steroid-dependent/refractory, steroid-resistant, and refractory cGVHD patients.

Patent Owner contends that "[t]he role of cytokines . . . was poorly understood: while some studies showed correlation of cytokine levels with cGVHD severity, others did not." PO Resp. 41. The evidence supports Patent Owner's position. *Compare* Ex. 1010, 172 ("In this study we have shown that patients who underwent BMT [bone marrow transplant] and subsequently developed cGVHD produce high or even extremely high levels of inflammatory cytokines as IL-β, IL-6, TNFα. Moreover, we found a good correlation between the severity of GVHD and the elevated cytokine levels."); *with* Ex. 2068, 336 ("Chronic GVHD has been observed in experimental models where acute GVHD is prevented with anti-TNF-α, suggesting that early release of TNF-α and conditioning-related tissue damage accelerate and amplify acute GVHD but are not relevant to the induction of chronic GVHD."); *and id.* at 337 ("These results would suggest that the proinflammatory cascade (IFNγ → TNF-α) does not operate during the pathophysiology of chronic GVHD, but further studies are needed."); Ex. 2055 ¶ 190 (Dr. Koreth testimony: "some studies showed correlation of cytokine levels with cGVHD severity, while others did not"). In view of the

uncertainty regarding the correlation of cytokines and cGVHD severity, Herman's teaching that ibrutinib inhibits cytokines does little to support a reasonable expectation of success.

Moreover, Herman teaches that one of the cytokines inhibited by ibrutinib is IL-10. Ex, 1004, 6291. The evidence supports that the POSA would have some concern that inhibiting IL-10 would be counterproductive in cGVHD patients because IL-10 was thought to be involved in suppressing immune responses. Ex. 2055 ¶¶ 164, 193 (Dr. Koreth's well-supported testimony that "numerous prior-art references . . . characterize IL-10 as an *anti*-inflammatory cytokine that could be used to prevent GVHD"); Ex. 2054, 8 ("IL-10 plays a key role in suppressing immune responses"); Ex. 1003, 4920 ("Regulatory B cells induce tolerance not only by acting as tolerogenic APCs, but also by producing well-known immunomodulatory cytokines, foremost IL-10 and TGF-β, which can suppress T-cell responses."). According to Dr. Koreth the teaching that ibrutinib inhibits IL–10 would have deterred one from using ibrutinib to treat cGVHD. Dr. Koreth concludes that "Herman counsels against the use of ibrutinib, a compound known to inhibit a beneficial cytokine, to treat cGVHD, further supporting the lack of any reasonable expectation of success to achieve the claimed invention." Ex. 2055 ¶ 193. We credit this well-supported, unrebutted testimony.

3. Contribution of the '085 publication to a reasonable expectation of success

The '085 publication discloses "[t]he development of drugs which inhibit BTK can have therapeutic significance in the treatment of both B cell-related hematological cancers . . . and autoimmune diseases." Ex. 1002 ¶ 2. The 085 publication also teaches that ibrutinib is a BTK

inhibitor (*id.* ¶ 4) and discloses "[o]ral pharmaceutical formulations of ibrutinib . . . and use of these formulations for the treatment of diseases treatable by ibrutinib such as . . . autoimmune diseases" (*id.*, abstract). Among the autoimmune diseases disclosed as treatable using the oral pharmaceutical formulations of the '085 publication is graft versus host disease. *Id.* ¶ 98.

We find that the teaching of the '085 publication regarding treatment of B cell related conditions does not meaningfully add to expectation of success fostered by Shimabukuro-Vornhagen's similar teaching that "B-cell depletion may . . . be a promising approach for the treatment of chronic GVHD," discussed *supra* p. 47–50. We also find that the '085 publication's teaching that ibrutinib can be used to treat GVHD does not meaningfully advance the expectation of success in the absence of supporting data, as discussed *supra* p. 35–42.

4. Conclusion regarding the reasonable expectation of success based on the combined teachings of the '085 publication, Shimabukuro-Vornhagen, and Herman

Our analysis of obviousness must take account of the factual background discussed above with respect to Ground 2, which reflects a poor understanding of cGVHD, an absence of predictive models and standardized measurement criteria, a multitude of unsuccessful treatments, unpredictability with respect to treatments, a dependence on trial and error testing, and an understanding that the claimed patient population was particularly difficult to treat. Starting from this background, a POSA would have been skeptical that any proposed treatments of steroid-dependent/refractory, steroid-resistant and/or refractory cGVHD patients would be successful.

Here, the evidence identified by Petitioner in connection with Ground 3, when considered against this background, is not sufficient to support a reasonable expectation of success. To summarize, Shimabukuro-Vornhagen supports a modest expectation that rituximab would be effective in treating the claimed patient population, but as applied to ibrutinib this modest expectation would have been diminished by reservations about whether results obtained using rituximab would extend to ibrutinib. Shimabukuro-Vornhagen also supports, at best, a weak expectation that drugs that target B cells would be effective in treating the claimed patient populations based on mechanism of action, but this expectation is diminished by evidence that drugs that target B and T cells (as well as a host of other drug candidates (*see* supra p. 38–39) had not been successful. Herman's teaching that ibrutinib inhibits cytokines does little to support a reasonable expectation of success, instead suggesting that ibrutinib may be detrimental because it targets the beneficial cytokine IL-10. Finally, the teaching of the '085 publication regarding B cells does not meaningfully add to the expectations fostered by Shimabukuro-Vornhagen similar teaching regarding B cell depletion and the teaching of the '085 publication that ibrutinib can be used to treat GVHD does not meaningfully advance an expectation of success in the absence of supporting data.

Considering all of the evidence and the arguments of record with respect to Ground 3, we find that Petitioner has not established by a preponderance of the evidence that a POSA would reasonably have expected ibrutinib to be successful in treating steroid-dependent/refractory, steroid-

resistant and/or refractory cGVHD patients.[20] Accordingly, we find that Petitioner has not established, by a preponderance of the evidence, that the combination of the '085 publication, Shimabukuro-Vornhagen, and Herman would have rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious.

V. GROUND 4: OBVIOUSNESS OVER THE COMBINATION OF THE '085 PUBLICATION, SHIMABUKURO-VORNHAGEN, AND UCKUN

Petitioner asserts that the combination of the '085 publication, Shimabukuro-Vornhagen, and Uckun renders claims 1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, and 55 of the '604 patent obvious. Pet. 62–66. We limit our discussion to whether the '085 publication, Shimabukuro-Vornhagen, and Uckun would have rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious because we have already determined that a preponderance of the evidence supports that the '085 publication anticipates claims 1, 6–10, 24, 35, 39, and 55. We have reviewed Petitioner's and Patent Owner's assertions, as well as the evidence of record, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 4, 13, 15, 28–31, 43–46 and 50–53 would have been obvious over the combination of the '085 publication, Shimabukuro-Vornhagen, and Herman.

[20] Patent Owner included extensive discussion of objective indicia of non-obviousness. PO Resp. 57–65. We have determined that it is not necessary to address this evidence in detail because it can only benefit the Patent Owner and we have already determined that the evidence does not support a finding that claims 4, 13, 15, 28–31, 43–46, and 50–53 would have been obvious over the '085 publication, Shimabukuro-Vornhagen, and Herman.

The factual background discussed above with respect to Ground 2 (*see supra.* p. 35–39) applies equally with respect to Ground 4. The following additional considerations apply to our discussion of ground 4.

A. Disclosures of the Asserted Prior Art

The ’085 Publication

The disclosure of the ’085 publication is discussed *supra* p. 9–10 and 43.

Shimabukuro-Vornhagen

The disclosure of Shimabukuro-Vornhagen is discussed *supra* p. 43. In addition to the disclosures of Shimabukuro-Vornhagen already discussed, Shimabukuro-Vornhagen discloses that several treatments useful for treating acute GVHD are also useful for treating chronic GVHD, including glucocorticoids, rituximab, statins, and ECP. Ex. 1003, 4919, 4921–22, 4924.

Uckun

Uckun discloses that “the covalent inhibitor PCI-32765 [ibrutinib] (Pharmacyclics) was developed as a selective and irreversible inhibitor of BTK targeting the Cysteine-481 residue in the active site.” Ex. 1005, 1464. Uckun further discloses that ibrutinib is a “potent nanomolar inhibitor of BTK.” *Id.* Uckun also discloses:

> Recent studies in a mouse BMT model demonstrated that the addition of a BTK inhibitor to the GVHD prophylaxis regimens significantly improves the survival outcome of allogeneic BMT. Notably, > 70% of BMT recipients treated with a BTK inhibitor-containing combination regimen remained alive throughout the 80-day observation period. Therefore, incorporation of BTK inhibitors in clinical GVHD prophylaxis regimens may improve the outcome by reducing the incidence of severe GVHD. We propose that the antileukemic activity of

> BTK inhibitors may enhance their ability to attenuate the severity of GVHD without increasing the risk of relapse post-BMT in clinical settings.

Id. at 1461. Uckun's teaching involves mice with acute rather than chronic GVHD. Ex. 1006 ¶ 148.

B. Analysis

As discussed above, claims 4, 13, and 15 depend from claim 1 and provide additional limitations concerning the patient to whom ibrutinib is administered. Claim 4 specifies that "the patient has steroid-dependent/refractory chronic GVHD." Claim 13 specifies that "the chronic GVHD is steroid resistant GVHD." And claim 15 specifies that "the chronic GVHD is refractory GVHD." Claims 28–31, 43–46, and 50–53 each depend from one of claims 4, 13, and 15.

Petitioner contends that "to the extent the Board finds that the '085 Publication alone did not anticipate or render obvious administering ibrutinib to treat ***chronic*** GVHD, that limitation would have been obvious over the '085 Publication in view of Shimabukuro-Vornhagen and Uckun." Pet. 62. Petitioner contends that: 1) the '085 publication "discloses administering therapeutically effective amounts of ibrutinib to treat GVHD," 2) Uckun discloses that ibrutinib is a "potent" BTK inhibitor and that "BTK inhibitors had been shown to treat acute GVHD in mice," and 3) Shimabukuro-Vornhagen teaches that "drugs that work for acute GVHD commonly work for chronic GVHD and vice versa." *Id.* at 65. Thus, according to Petitioner, "when these three references are combined, a POSA would have had a reasonable expectation that administering ibrutinib, at the

doses disclosed in the '085 Publication, would have treated a patient's chronic GVHD."[21] *Id.*

Patent Owner argues:

> Uckun's disclosure of a *different* BTK inhibitor used for *prophylaxis* in a mouse model of *acute* GVHD cannot establish a reasonable expectation of success for the asserted combination because: (1) results from mouse models failed to translate to clinical cGVHD in humans; (2) aGVHD cannot be conflated with cGVHD, and prophylaxis cannot be conflated with treatment; (3) LFM-A13 had not been shown to *treat* aGVHD or cGVHD in mouse models or in the clinic; (4) the cited LFM-A13 mouse study does not establish efficacy with BTK inhibitors, even for prophylaxis; and (5) even if LFM-A13 had activity in GVHD, its simultaneous inhibition of other protein kinases obfuscates any potential connection to BTK inhibition. EX2055, ¶197.

PO. Resp. 44. We agree with Patent Owner that the record does not support that the POSA would reasonably have expected, based on the '085 publication, Shimabukuro-Vornhagen, and Uckun, that ibrutinib could be used to successfully treat steroid-resistant, steroid-dependent and refractory cGVHD patients.

1. Contribution of Uckun and Shimabukuro-Vornhagen to a reasonable expectation of success

Uckun discloses that "[r]ecent studies in a mouse BMT model demonstrated that the addition of a BTK inhibitor to the GVHD prophylaxis regimens significantly improves the survival outcome of allogeneic BMT." Ex. 1005, 1461. For the reasons discussed below, we find that the record does not support that this teaching would have contributed significantly to

[21] Petitioner does not specifically address the patient populations recited in claims 4, 13, and 15 as they relate to the combined teachings of the '085 publication, Shimabukuro-Vornhagen, and Uckun in the Petition.

the expectation of a POSA that administering ibrutinib would successfully treat patients with steroid-dependent/refractory, steroid-resistant, or refractory cGVHD.

First, the evidence supports that mouse models were generally not accepted as supporting treatment of cGVHD in humans. Ex. 2003, abstract ("no animal model fully replicates all of the features of CGVHD in humans"); *id.* at 84–85 (discussing mouse model noting, "the relevance of this model for human CGVHD is questionable"); Ex. 2056, 92:21–95:21 (Dr. Ferrara's deposition testimony discussing deficiencies of animal models with respect to cGVHD); Ex. 2008, 859 ("Because models of CGVHD do not replicate human disease and the models of AGVHD, it is difficult to determine whether these results can be applicable to clinical GVHD prevention and treatment."); Ex. 2066 ¶ 206 (Dr. Koreth testimony that "it was widely acknowledged by researchers, including Dr. Ferrara, that extant mouse models correlated poorly to clinical manifestations of cGVHD in patients").

Second, the evidence supports that success in preventing cGVHD may not extend to success in treating cGVHD.[22] Ex. 2059, 207 ("Disparate results of intervention to prevent and/or treat aGVHD or cGVHD are

[22] The parties agree that "treatment" as recited in the claims excludes prophylaxis. Pet. 16 n 2; *see also,* PO Resp. 15. We note that the '085 publication discloses the use of a BTK inhibitor – ibrutinib – to treat GVHD and defines "treatment" to include "arresting or reducing the development of the disease or its clinical symptoms" or "causing regression of the disease or its clinical symptoms." Ex. 1002 ¶¶ 98, 116–119. However, as discussed above, the '085 publication lacks data to support this teaching. Accordingly, in Ground 4, Petitioner relies on Uckun as providing supporting data. Uckun does not define prophylaxis to include treatment.

common."); Ex. 2004, 254–259 (distinguishing approaches for prophylaxis and treatment); Ex. 2055, ¶205.[23]

Third, we agree with Petitioner that Shimabukuro-Vornhagen supports that many treatments were used to treat both acute GVHD and chronic GVHD, including steroids, rituximab, statins, and extracorporeal photopheresis ("ECP"). *See* Ex. 1006 ¶ 32; Ex. 1003, 4919, 4921–22, 4924. Nonetheless, the evidence also supports that drugs that were used for acute GVHD were known to fail when used for chronic GVHD. Ex. 2010, 1 ("While there are some lessons that can be translated from basic and clinical studies of acute GVHD, several lines of evidence suggest chronic GVHD is not simply a continuation of acute GVHD, and that separate approaches will be required for its prevention and management"); Ex. 2008, 854 ("[A]lthough AGVHD and CGVHD are similar in some respects, it seems likely that the two diseases have different initiation requirements and pathogenic mechanisms. More importantly from the experimental view, it is not obvious whether findings based on the AGVHD models apply to CGVHD syndrome."); Ex. 2055 ¶ 205 (Dr. Koreth's testimony regarding extension of aGVHD treatments to cGVHD).

Fourth, Uckun teaches that "incorporation of BTK inhibitors ***in clinical GVHD prophylaxis regimens*** may improve the outcome by reducing the incidence of sever GVHD." Ex. 1005, 1461 (emphasis added). This statement is a conclusion drawn directly from the preceding sentence,

[23] During prosecution, the Examiner recognized the distinction between treating and preventing GVHD. Ex. 1021, 7 (rejecting then pending claims as lacking written description support because the specification "while being enabling for only a treatment method . . . does not reasonably provide enablement for a method of preventing *'the occurrence of graft versus host disease*").

which states: "Notably, > 70% of BMT recipients ***treated with a BTK inhibitor-containing combination regimen*** remained alive throughout the 80-day observation period." *Id.* (emphasis added). Thus, Uckun's teaching is not that a BTK inhibitor by itself is beneficial, but rather that a BTK inhibitor is beneficial when added to a *combination prophylaxis regimen*. Indeed, the data on which Uckun relies shows that treatment with the BTK inhibitor LFM-A13 had a limited effect, with only 2% of the treated animals surviving 80 days. Ex. 1012, 824; Ex. 2055 ¶ 200 (Dr. Koreth discussing same). By comparison, 73% of mice treated with both the BTK inhibitor and a Janus kinase 3 ("JK3") inhibitor survived 80 days. Ex. 1012, 824. We recognize, that claims 4, 13, and 15 are "comprising" claims, and do thus not preclude the addition of another treatment agent. But Petitioner's obviousness theory is predicated only on using a BTK inhibitor, making no mention of combination therapy or, more specifically, of JK3 inhibitors. Pet. 62–66.

2. Contribution of the '085 publication to a reasonable expectation of success

As discussed above in connection with Grounds 2 and 3, the teaching of the '085 publication that ibrutinib can be used to treat GVHD does not meaningfully advance an expectation of success in the absence of supporting data. *See supra* p. 39–42 and 54–55.

3. Conclusion regarding the reasonable expectation of success based on the combined teachings of the '085 publication, Shimabukuro-Vornhagen, and Uckun

Our analysis of obviousness must take account of the factual background discussed above with respect to Ground 2, which reflects a poor understanding of cGVHD, an absence of predictive models and standardized

measurement criteria, a multitude of unsuccessful treatments, unpredictability with respect to treatments, a dependence on trial and error testing, and an understanding that the claimed patient population was particularly difficult to treat. Starting from this background, a POSA would have been skeptical that any proposed treatments of steroid-dependent/refractory, steroid-resistant and/or refractory cGVHD patients would be successful.

Here, the evidence identified by Petitioner in connection with Ground 4, when considered against this background, is not sufficient to support a reasonable expectation of success. To summarize, finding support for the obviousness of the claimed method in Uckun's disclosure requires the POSA to: extend mouse models to human patients; extend teachings on prevention to treatment; extend teachings on acute GVHD to the specifically claimed population of cGVHD patients; and, based on the obviousness theory set forth by Petitioner, extend teachings on combination therapy using a BTK inhibitor to administration of BTK alone, or at least without a JK3 inhibitor. Considering all of the evidence together, we find that the teaching in Uckun regarding the use of BTK in prophylaxis regimens is too attenuated from treatment of patients with steroid-dependent/refractory, steroid-resistant, or refractory cGVHD to meaningful contribute to a reasonable expectation of success.

The other references cited in Ground 4 also do not support an expectation of success. Petitioner relied on Shimabukuro-Vornhagen in Ground 4 only for the teaching that drugs that treat acute GVHD have also been used to treat chronic GVHD. This teaching was discussed above. The teaching of the '085 publication that ibrutinib can be used to treat GVHD

does not meaningfully advance an expectation of success in the absence of supporting data for the reasons discussed above. *See supra* p. 39–42 and 54–55.

Considering all of the evidence and the arguments of record with respect to Ground 4, we find that Petitioner has not established by a preponderance of the evidence that a POSA would reasonably have expected ibrutinib to be successful in treating steroid-dependent/refractory, steroid-resistant and/or refractory cGVHD patients.[24] Accordingly, we find that Petitioner has not established the combination of the '085 publication, Shimabukuro-Vornhagen, and Uckun would have rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious.

VI. PATENT OWNER'S MOTION TO STRIKE

Patent Owner moves to strike two arguments made in Petitioner's Reply on the basis that they present new arguments. Mot. 1. First, Patent Owner requests that we strike Petitioner's argument that the '085 publication expressly discloses administration of ibrutinib to the patient populations recited in claims 4, 13, and 15. *Id.* at 1–3 (identifying the briefing at Pet. Reply 9–10). Second, Patent Owner requests that we strike Petitioner's argument that the '085 publication expressly discloses the efficacy limitations recited in claims 6–8, 29–31, 44–46, and 51–53. *Id.* at 3 (identifying the briefing at Pet. Reply 10–11).

[24] Patent Owner included extensive discussion of objective indicia of non-obviousness. PO Resp. 57–65. We have determined that it is not necessary to address this evidence in detail because it can only benefit the Patent Owner and we have already determined that the evidence does not support a finding that claims 4, 13, 15, 28–31, 43–46, and 50–53 would have been obvious over the '085 publication, Shimabukuro-Vornhagen, and Uckun.

We addressed Petitioner's argument that the '085 publication expressly discloses administration of ibrutinib to the claimed patient populations in the context of our discussion of Ground 1, concluding both that Petitioner's argument was new, and thus should not be considered, and also that it lacked merit. *See supra* p. 22–27. We discern no need to take the additional step of striking this portion of Petitioner's Reply brief. *See* Trial Practice Guide August 2018 update, 17–18 ("In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply. As such, striking the entirety or a portion of a party's brief is an exceptional remedy that the Board expects will be granted rarely."). Accordingly, we deny Patent Owner's motion to strike this portion of Petitioner's briefing.

We did not consider Petitioner's argument that the '085 publication expressly discloses the efficacy limitations recited in certain of the challenged claims because we found that these limitations were inherently disclosed. Accordingly, we dismiss this portion of Patent Owner's Motion to Strike as moot.

VII. CONSTITUTIONAL CHALLENGE

Patent Owner states: "Given *Arthrex, Inc. v. Smith & Nephew Inc.*, 941 F.3d 1320 (Fed. Cir. 2019) and subsequent Federal Circuit authority, Patent Owner challenges the constitutionality of this proceeding and authority of the panel to adjudicate this dispute." PO. Resp. 66.

We decline to consider Patent Owner's constitutional challenge as the issue has been addressed by the Federal Circuit in *Arthrex*. *See Arthrex*, 941

F.3d at 1337 ("This as-applied severance . . . cures the constitutional violation . . . .").

VIII. CONCLUSION[25]

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	102	'085 publication	1, 6–10, 24, 35, 39, 55	4, 13, 15, 28–31, 43–46, 50–53
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	103[26]	'085 publication		4, 13, 15, 28–31, 43–46, 50–53
1, 4, 6–10, 13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55	103	'085 publication, Shimabukuro-Vornhagen, Herman		4, 13, 15, 28–31, 43–46, 50–53
1, 4, 6–10,	103	'085 publication,		4, 13, 15, 28–

[25] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

[26] We limited our analysis of Petitioner's three obviousness grounds to whether the cited art rendered claims 4, 13, 15, 28–31, 43–46 and 50–53 obvious because we had already determined that a preponderance of the evidence supported that the '085 publication anticipated claims 1, 6–10, 24, 35, 39, and 55.

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
13, 15, 24, 28–31, 35, 39, 43–46, 50–53, 55		Shimabukuro-Vornhagen, Uckun		31, 43–46, 50–53
Overall Outcome			1, 6–10, 24, 35, 39, 55	4, 13, 15, 28–31, 43–46, 50–53

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1, 6–10, 24, 35, 39, and 55 of the '604 patent are unpatentable;

FURTHER ORDERED that Petitioner has not proven by a preponderance of the evidence that claims 4, 13, 15, 28–31, 43–46, 50–53 are unpatenable;

FURTHER ORDERED that Patent Owner's motion to strike is denied in part and dismissed in part;

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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