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Paper No. 13
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
APOTEX INC., APOTEX CORP.,
TEVA PHARMACEUTICALS USA, INC.,
FRESENIUS KABI USA, LLC, and WOCKHARDT BIO AG,
Petitioner,

v.

ELI LILLY & COMPANY,
Patent Owner.

Case IPR2016-00237[1]
Patent 7,772,209 B2

Before JACQUELINE WRIGHT BONILLA, MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judges*, and LORA M. GREEN, *Administrative Patent Judge*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining That Claims 1–22 Have Not Been Shown to Be Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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[1] Cases IPR2016-01190, IPR2016-01335, and IPR2016-01341 have been joined with the instant proceeding.

I. INTRODUCTION

Neptune Generics, LLC, filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 7,772,209 B2 (Ex. 1001, "the '209 patent"). Paper 1 ("Pet."). Eli Lilly & Company ("Patent Owner" or "Lilly") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–22 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on June 3, 2016, as to all of the challenged claims of the '209 patent. Paper 13 ("Institution Decision" or "Dec. Inst.").

Thereafter, other parties filed three additional Petitions challenging the same claims based on the same ground of unpatentability over the same prior art as those instituted by the Board in the instant case, as well as motions for joinder. Specifically, Apotex Inc. and Apotex Corp. requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01190, and joinder to the instant proceeding. IPR2016-01190, Papers 2 and 3. On October 6, 2016, the Board instituted *inter partes* review in that case and granted joinder. IPR2016-01190, Paper 11. Wockhardt Bio AG also requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01335, as well as joinder to the instant proceeding. IPR2016-01335, Papers 1 and 3. *Inter partes* review was instituted in that case and joinder granted on November 18, 2016. IPR2016-01335, Paper 8. Finally, Teva Pharmaceuticals USA, Inc., and Fresenius Kabi USA, LLC, also requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01341, and joinder to the instant proceeding. IPR2016-01341, Papers 2 and 3. *Inter*

partes review was instituted and joinder granted on October 6, 2016. IPR2016-01341, Paper 10. We collectively refer to all enjoined Petitioners in this Final Written Decision as "Petitioner."

Patent Owner filed a Response (Paper 33, "PO Resp."), Petitioner filed a Reply (Paper 48), and Patent Owner filed a Sur-reply (Paper 63). Petitioner filed a Motion to Exclude (Paper 57, "Mot. Exclude"), to which Patent Owner filed an Opposition (Paper 67, "Opp. Mot. Exclude"), and Petitioner filed a Reply (Paper 74). Oral hearing was held on March 16, 2017, and a transcript of that hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Based on the record before us, we conclude that Petitioner has failed to demonstrate by a preponderance of the evidence that claims 1–22 of the '209 patent are unpatentable. We also *deny* Petitioner's Motion to Exclude.

A. Related Proceedings

The '209 patent is the subject of litigation in the U.S. District Court for the Southern District of Indiana, including *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, No. 1:10-cv-1376 (S.D. Ind.) (filed Oct. 29, 2010). Pet. 2–3; Prelim. Resp. 2.

The ’209 patent also has been challenged in IPR2016-00240 by Neptune Generics, LLC, and in IPR2016-00318 by Sandoz Inc. Proceedings IPR2016-01191, IPR2016-01337, and IPR2016-01343 have been joined with IPR2016-00240, and proceedings IPR2016-01393, IPR2016-01340, and IPR2016-01429 have been joined with IPR2016-00318.

B. The ’209 Patent

The ’209 patent issued on August 10, 2010, listing Clet Niyikiza as the sole inventor. Ex. 1001. The ’209 patent claims priority to a series of applications, the earliest of which was filed on June 30, 2000. *Id.* at 1:2–10.

“As cancer cells are actively proliferating, they require large quantities of DNA and RNA.” Ex. 1025 ¶ 67. Antifolates are a well-studied class of antineoplastic agents that inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways. Ex. 1001, 1:19–20, 1:36–41. Because antifolates interfere with DNA and RNA synthesis, antifolates are used as chemotherapeutic drugs to treat certain types of cancer. Ex. 1025 ¶ 67.

A limitation on the use of antifolate drugs is “that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients.” Ex. 1001, 1:62–64. Homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of certain antifolate enzyme inhibitors. *Id*. at 2:16–26. The ’209 patent states that folic acid has been shown to lower homocysteine levels. *Id*. Additionally, the patent states that it was known in the art to treat and prevent cardiovascular disease with a combination of folic acid and vitamin B12, but that “the use of the combination for the treatment of toxicity

associated with the administration of antifolate drugs was unknown heretofore." *Id*. at 2:50–54.

The '209 patent describes "[a] method of administering an antifolate to a mammal in need thereof." *Id.*, Abstract. The method is said to improve the therapeutic utility of antifolate drugs by administering a methylmalonic acid ("MMA") lowering agent, such as vitamin B12, to the host undergoing treatment. *Id*. at 2:37–46. The '209 patent also states that a combination of a MMA lowering agent, such as vitamin B12, and folic acid "synergistically reduces the toxic events associated with the administration of antifolate drugs." *Id*. at 2:47–50.

The term antifolate is said to encompass chemical compounds that inhibit at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways. *Id*. at 4:28–34. Pemetrexed disodium is the most preferred antifolate for the '209 patent. *Id*. at 4:28–43. Pemetrexed is also referred to in the art as the "multitargeted antifolate" ("MTA").[2] Ex. 1022, 129,[3] Abstract 620P.

C. Illustrative Claims

Petitioner challenges claims 1–22 of the '209 patent. Claims 1 and 12 are independent, and are reproduced below:

> 1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by

[2] We use "pemetrexed" and "MTA" interchangeably throughout this Decision.

[3] We note that, unless otherwise indicated, the page numbers refer to the page numbers of the original references, and not to those added by a party.

administering an effective amount of pemetrexed disodium, wherein

the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.

12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;

b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium.

Ex. 1001, 10:56–65, 11:25–12:4.

D. Prior Litigation

On March 31, 2014, the U.S. District Court for the Southern District of Indiana upheld claims 9, 10, 12, 14, 15, 18, 19, and 21 of the ’209 patent as unobvious under the clear and convincing evidence evidentiary standard. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, No. 1:10-cv-01376-TWP-DKL, 2014 WL 1350129, at *1 (S.D. Ind. Mar. 31, 2014), *aff’d*, 845 F.3d 1357 (Fed. Cir. 2017). The court summarized the ’209 patent as describing a method of co-administering folic acid and vitamin B12 with pemetrexed, which is an antifolate and chemotherapy drug marketed under the trade name ALIMTA®, to reduce side effects referred to as “toxicities.” *Id.* at *1–2. The court concluded that there was not clear and convincing evidence that the ordinary artisan would have had reason to administer (1) folic acid

pretreatment with pemetrexed, (2) vitamin B12 pretreatment with pemetrexed, or (3) each of folic acid and vitamin B12 according to the claimed doses and schedules. *Id.* at *6. Additionally, the court found that secondary considerations—namely, skepticism, failure of others, and unexpected results—supported the conclusion that the claims at issue were not obvious. *Id.* at *14–16.

In making the first finding—that the administration of folic acid with pemetrexed was not obvious—the court discussed Worzalla,[4, 5] Hammond I,[6] Rinaldi,[7] and the '974 patent.[8] *Id.* at *6–9. Both Worzalla and Hammond I reported the results of oncology research involving the administration of folic acid with pemetrexed—to mice in Worzalla, and to Phase I patients in Hammond I. *Id.* at *6–8. Although both studies indicated a reduction of toxicity associated with pemetrexed, the court concluded that the ordinary artisan would not have had the goal of reducing toxicity at the expense of

[4] John F. Worzalla et al., *Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514*, 18 ANTICANCER RES. 3235 (1998) (Ex. 1005) ("Worzalla").

[5] Note that the exhibit numbers referenced in the footnotes containing the citation to reference refer to the reference's exhibit numbers in the instant proceeding.

[6] L. Hammond et al., *A Phase I and Pharmacokinetic (PK) Study of the Multitargeted Antifolate (MTA, LY231514) with Folic Acid (FA)*, 9 ANNALS ONCOLOGY 129, Abstract 620P (Supp. 4 1998) (Ex. 1022) ("Hammond I").

[7] D.A. Rinaldi et al., *A Phase I Evaluation of LY231514, A Novel Multi-Targeted Antifolate, Administered Every 21 Days*, PROC. AM. SOC'Y CLINICAL ONCOLOGY, May 18–21, 1996, at 489, Abstract 1559 (Ex. 2022) ("Rinaldi").

[8] Grindey et al., U.S. Patent No. 5,217,974, issued June 8, 1993 (Ex. 1009) ("the '974 patent").

either reducing the efficacy of pemetrexed or requiring higher doses of the drug. *Id.* at *8. In this regard, Rinaldi published the results of an unsupplemented Phase I pemetrexed study, and showed better efficacy than Hammond I's study. *Id.* The court also found that, when supplementing pemetrexed with folic acid, much higher doses of pemetrexed would have been required, which would have raised other concerns such as kidney toxicity. *Id.* at *7–8. Furthermore, the court distinguished the '974 patent because it did not mention pemetrexed, but instead specifically considered folic acid pretreatment with a different drug, lometrexol. *Id.* at 9.

In making the second finding—that the administration of vitamin B12 with pemetrexed was not obvious—the court considered Niyikiza[9] and Niyikiza II[10] (collectively, the "Niyikiza Abstracts"). *Id.* at *10. The Niyikiza Abstracts showed a correlation between pemetrexed toxicities and patients' levels of homocysteine. *Id.* at *4, *10. As the court explained, however, elevated homocysteine levels, standing alone, did not indicate a vitamin B12 deficiency—instead, *both* elevated homocysteine *and* elevated MMA levels were necessary to establish a vitamin B12 deficiency. *Id.* at *4. The court further explained that in the Niyikiza Abstracts, there was no correlation between toxicity and other measured variables, including MMA, which suggested at the time that there was no correlation between toxicity

[9] C. Niyikiza et al., *MTA (LY231514): Relationship of Vitamin Metabolite Profile, Drug Exposure, and Other Patient Characteristics To Toxicity*, 9 ANNALS ONCOLOGY 126, Abstract 609P (Supp. 4 1998) (Ex. 1008) ("Niyikiza").

[10] C. Niyikiza et al., *LY231514 (MTA): Relationship of Vitamin Metabolite Profile To Toxicity*, PROC. AM. SOC'Y CLINICAL ONCOLOGY, May 16–19, 1998, at 558a, Abstract 2139 (Ex. 2015) ("Niyikiza II").

and vitamin B12 levels. *Id.* The court therefore found that the ordinary artisan would have concluded that vitamin B12 deficiency was not the problem in pemetrexed toxicity. *Id.* at *10.

Also, the court was not persuaded by evidence indicating that vitamin B12 was routinely added to folic acid pretreatment to prevent "masking," a problem in which a vitamin B12 deficiency was misdiagnosed as a folate deficiency. *Id.* at *9–10. The court found this evidence to be in the context of treating rheumatoid arthritis, where vitamin B12's interference with the antiproliferative effects of the active drug was less of a concern than in treating cancer. *Id.* at *10. Likewise, the court described other evidence showing that in patients who were vitamin B12 deficient, folate became "trapped" in cells, and when patients were later administered vitamin B12, that administration released the folates from the trap, counteracting the efficacy of an antifolate drug. *Id.* at *11.

In making the third finding—that the claimed doses and schedules would not have been obvious—the court found no prior art disclosure of the ranges of folic acid and vitamin B12, as set forth in the claims at issue, for use with pemetrexed in the treatment of cancer. *Id.* at *13. In particular, the court explained that no prior art references disclosed *any* amount of vitamin B12 pretreatment for use with an antifolate in treating cancer. *Id.*

On January 12, 2017, the U.S. Court of Appeals for the Federal Circuit affirmed the district court. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357 (Fed. Cir. 2017). Specifically, the Federal Circuit affirmed the district court's findings that the ordinary artisan would not have been motivated to use vitamin B12 pretreatment with pemetrexed, let alone at the appropriate doses and schedules of vitamin B12 pretreatment. *Id.* at

1373. The Federal Circuit did not reach the issue of whether the prior art provided a motivation for the use of folic acid pretreatment to counter pemetrexed toxicity. *Id.* at 1373–74.

The Federal Circuit summarized the district court's findings that the ordinary artisan "would have concluded that vitamin B_{12} deficiency was not the problem in pemetrexed toxicity" and "would not have used vitamin B_{12} supplementation to address antifolate toxicities because of 'concern[ ] about . . . a reduction of efficacy of the antifolate' treatment." *Id.* at 1373 (alteration in original) (quoting *Eli Lilly*, 2014 WL 1350129, at *10–11). Like the district court, the Federal Circuit explained that elevated homocysteine levels alone did not specifically indicate a vitamin B12 deficiency—instead, MMA levels specifically indicated a vitamin B12 deficiency. *Id.* at 1373. The Federal Circuit then quoted from Niyikiza II, that "no correlation between toxicity . . . and [MMA levels] was seen." *Id.* (alteration in original).

Accordingly, the Federal Circuit found a "missing link between vitamin B_{12} deficiency and pemetrexed toxicity" that was not overcome by the evidence of record. *Id.* That is, there was no evidence that even if folic acid supplementation was known to improve pemetrexed toxicity, the ordinary artisan would have thought the same of vitamin B12. *Id.* at 1374. Also, expert testimony provided that vitamin B12 pretreatment would have affected pemetrexed's efficacy by "having to increase the [antifolate] dose to get the same activity" of cancer treatment, which the ordinary artisan would have viewed as "a problem." *Id.* (alteration in original) (quoting Ex. 1051, 138:7–8).

The Federal Circuit found that two prior art references, one of them being Calvert 1999,[11] which Petitioner cites as evidence as to the knowledge of the ordinary artisan in this proceeding, "merely note in passing that vitamin B12 can be related to homocysteine levels and folate biochemical pathways." *Id.* at 1375; Tr. 147:14–19. There was no testimony that those references would have provided a motivation to use vitamin B12 pretreatment with pemetrexed, when viewed with the evidence of the gaps and concerns in the prior art that were specifically identified by the Federal Circuit. 845 F.3d at 1375.

The Federal Circuit also addressed the doses and schedules and determined that there was only evidence of vitamin B12 doses and schedules that are "routine" in different medical contexts. *Id.* at 1374. The Federal Circuit found no evidence that the ordinary artisan would have applied those doses and schedules wholesale to the context of pemetrexed treatment. *Id.*

E. Instituted Challenge

We instituted trial based on the following ground of unpatentability (Dec. Inst. 19):

References	**Basis**	**Claims Challenged**
Niyikiza, the '974 patent, and EP 005[12]	§ 103(a)	1–22

[11] Hilary Calvert, *An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents*, SEMINARS ONCOLOGY, Apr. 1999, at 3 (Ex. 1014) ("Calvert 1999").

[12] Willem Jacob Serfontein, EP 0 595 005 A1, published May 4, 1994 (Ex. 1010) ("EP 005").

Petitioner relies also on the Declaration of W. Archie Bleyer, M.D., FRCP (Ex. 1025), the Supplemental Declaration of Dr. Bleyer (Ex. 1077), as well as the Reply Declarations of David W. Feigal, Jr., M.D., M.P.H. (Ex. 1080) and Joel B. Mason, M.D. (Ex. 1078).

Patent Owner relies on the Declarations of Steven H. Zeisel, M.D., Ph.D. (Ex. 2118), and Bruce A. Chabner, M.D. (Ex. 2120).

II. ANALYSIS

Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain why Petitioner has failed to meet its burden with respect to the challenged claims.

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–45 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their

plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Institution Decision, we determined that none of the terms in the challenged claims required express construction at that time. Dec. Inst. 10 (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy)). In its Response, Patent Owner agrees that none of the claim terms require construction (PO Resp. 16),[13] and Petitioner does not dispute that in its Reply. Thus, we again determine that none of the terms in the challenged claims require express construction.

B. Level of Ordinary Skill in the Art

Petitioner contends:

> A person of ordinary skill in the art ("POSA") in oncology as of June 30, 1999—the earliest possible priority date for the '209 Patent—would be "a medical doctor with an M.D. degree who has significant experience in treating cancer patients, and a significant understanding of antineoplastic agents, including antifolates and their efficacies, safety, adverse effects, etc." (Ex. 1025 ¶ 20.) "A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others on the team, to solve a given problem. For example, an expert in nutrition, an expert in hematology, a basic scientist

[13] Patent Owner notes that both it and Petitioner agree that a "patient" is "a human undergoing medical treatment," which is disputed in IPR2016-00318. PO Resp. 16. For purposes of this Decision, we do not disagree with that claim construction, and, moreover, as that term is not in dispute in this proceeding, do not find a need to construe it here.

> with expertise in biochemistry, and a clinician may be part of the team." (*Id.* ¶ 21; *see also* Ex. 1028 at 9.)

Pet. 24–25.

Patent Owner responds, relying on its expert, Dr. Chabner, that the ordinary artisan

> would be a "medical doctor who specializes in oncology, specifically medical oncology," and "would have knowledge and experience concerning the use of chemotherapy agents, including antifolates, in the treatment of cancer, as well as knowledge and experience regarding the management of toxicities associated with such treatment." [Ex. 2120] ¶ 23. Dr. Chabner added that the POSA would have an "understanding of how nutritional issues relate to the use of chemotherapy agents," as well as "an understanding of the interrelationships between antifolates, the folic acid pathway, and pathways related to vitamin B_{12}." *Id*. ¶ 25.

PO Resp. 14–15. In particular, Patent Owner disagrees with Petitioner's expert, Dr. Bleyer, that the ordinary artisan would defer to a nutritionist in determining whether to treat a cancer patient with vitamins, but asserts that such decisions would be made by the medical oncologist. *Id.* at 15 (citing Ex. 2120 ¶ 24; Ex. 2118 ¶ 17).

We adopt Patent Owner's statement of the level of ordinary skill in the art, as we find that the ordinary artisan would be an oncologist, and although that oncologist may have access to experts in nutrition, the oncologist would make final decisions as to treatment. Moreover, we note that, in this case, the level of ordinary skill in the art is reflected by the prior art of record. *Cf. Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). In addition, our analysis would be the same under either Petitioner's or Patent Owner's definition of the ordinary artisan.

C. Obviousness over Niyikiza, the '974 patent, and EP 005

Petitioner contends that claims 1–22 are rendered obvious by the combination of Niyikiza, the '974 patent, and EP 005. Pet. 25–51. Patent Owner disagrees with Petitioner's contentions, asserting that the Petition fails to demonstrate the obviousness of the challenged claims by a preponderance of the evidence. PO Resp. 16–54.

i. Overview of the Prior Art Relied Upon

We find the following as to the teachings of the relevant prior art.

a. Niyikiza (Ex. 1008)

Niyikiza, a meeting abstract, states that MTA (pemetrexed) "is a novel multitargeted antifolate with inhibitory activity against multiple enzymes." Ex. 1008, 126, Abstract 609P. According to Niyikiza, "[h]istorical data on other antifolates have suggested that a patient's nutritional status may play a role in the likelihood of experiencing severe toxicity." *Id.* Thus, Niyikiza states that the "purpose of th[e] study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following retreatment with MTA." *Id.*

Niyikiza describes treating 139 patients with tumors in a Phase II study with MTA and monitoring the patients for homocysteine, cystathionine, and methylmalonic acid ("MMA") levels. *Id*. Toxicities resulting from the MTA treatment were found to be predictable from pretreatment homocysteine levels. *Id*. at 127. In particular, Niyikiza found that "[e]levated baseline homocysteine levels (≥ 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA," and that "[h]omocysteine was found to be better than albumin at predicting toxicity." *Id.* Niyikiza states that further studies are underway

in patients with renal impairment or patients who received prior cisplatin. *Id*.

b. The '974 patent (Ex. 1009)

The '974 patent describes the administration of a folate binding protein binding agent in conjunction with the use of an antifolate. Ex. 1009, Abstract, 1:54–58, 2:60–65. In particular, the '974 patent teaches "a method for improving the therapeutic utility of [glycinamide ribonucleotide ("GAR")]-transformylase inhibitors and other antifolates by co-administering a [folate binding protein ("FBP")] binding agent to the host under going treatment." *Id.* at 1:54–58. The preferred antifolate of the '974 patent is lometrexol, which is "a potent antitumor agent, especially against solid tumors such as colorectal, lung, breast, head and neck and pancreatic." *Id.* at 1:34–37. The '974 patent teaches, however, that lometrexol has undesirable side effects, such as anorexia, weight loss, mucositis, leukopenia, anemia, hypoactivity, and dehydration. *Id.* at 1:40–45.

In the method of the '974 patent, the FBP binding agent is administered to a mammal prior to treatment with an antifolate. *Id*. at 6:22–24. A preferred embodiment involves administering about 1 mg to about 5 mg of folic acid as the FBP binding agent, with the folic acid administered orally about 1 to 24 hours prior to treatment with lometrexol. *Id*. at 6:37–42. Multiple doses of folic acid may be administered up to weeks before treatment to ensure that the folate binding protein is sufficiently bound. *Id*. at 6:32–37. The '974 patent teaches:

> It should be noted that the FBP binding agent is not an antitumor agent and that the pretreatment of a mammal with a FBP binding agent is not a synergistic or potentiating effect. Rather, by having substantially bound the folate binding protein with a FBP

> binding agent prior to administration of the GAR-transformylase inhibitor or other antifolate, the toxic effects of such subsequent treatment are greatly reduced without affecting the therapeutic efficacy.

Id. at 6:48–56.

The '974 patent teaches testing on mice in which a mammary carcinoma has been introduced. *Id.* at 6:61–64. The '974 patent states that the data obtained using those mice establish that for tumor bearing mice that are maintained on a folic acid free diet prior to treatment with lometrexol, the toxicity of the lometrexol is very large. *Id.* at 8:15–20. Very low doses of folic acid, however, "partially reversed drug toxicity and improved antitumor activity," and larger doses "dramatically reduced lometrexol toxicity and markedly improved antitumor activity." *Id.* at 8:20–26.

The '974 patent also reports results with a single patient with nasalpharyngeal carcinoma supplemented with folic acid tolerated treatment with lometrexol for up to twelve months, showing no clinical evidence of the disease after that time. *Id.* at 8:49–57. The '974 patent teaches that those results "are consistent with the animal studies." *Id.* at 8:57–58.

c. EP 005 (Ex. 1010)

EP 005 is drawn to pharmaceutical preparations for lowering blood and tissue levels of homocysteine and counteracting harmful effects associated with homocysteine. Ex. 1010, Abstract, 2:1–3. According to EP 005, elevated homocysteine levels are correlated with "some of the princip[al] causes of morbidity and mortality in the Western world," such as myocardial and cerebral infarction. *Id.* at 2:4–6. Elevated homocysteine levels are highly undesirable and normalization of elevated levels constitutes a therapeutic goal. *Id.* at 3:7–9.

Three pathways are said to exist to control homocysteine including remethylation to methionine, which requires folate, as well asvitamin B12 as a co-factor. *Id*. at 2:25–30. EP 005 identifies a number of publications that are said to describe the relationship between vitamin B12 and folate levels individually and blood levels of homocysteine. *Id*. at 3:37–45. EP 005 seeks to lower total homocysteine blood levels elevated by any known cause, including drugs that induce elevated homocysteine levels, such as methotrexate, a well-known antifolate. *Id*. at 4:43–48; Ex. 1025 ¶ 64. EP 005 teaches that other situations in which blood homocysteine may be elevated include leukemia and other cancers. Ex. 1010, 9:54–56.

EP 005 discloses a pharmaceutical preparation comprising vitamin B6, folate and vitamin B12, for prophylaxis or treatment of elevated levels of homocysteine in a patient. *Id*. at 4:37–42. According to EP 005, for purposes of controlling blood homocysteine levels, the combination of folate, vitamin B12, and vitamin B6 produces advantageous effects that go substantially beyond what would be expected from a simple additive effect of the action of these compounds. *Id*. at 11:20–23. In addition, EP 005 teaches that "an unexpected synergism exists when vitamin B12, folate and [vitamin B6] are given concurrently," which may result in better control of blood homocysteine levels at lower dosages of each. *Id.* at 11:23–26.

A suitable daily dosage of the pharmaceutical preparation is described in the table reproduced below:

Formulation type	PL		Folate		B12	
	Range mg	Preferred mg	Range mg	Preferred mg	Range mg	Preferred mg
Normal (no absorption problem)	2-5	5	0,2-15	1,0	0.1-2	0.5
Special (to overcome absorption problems)	2-50	5	2-15	5	0.2-5	1,0

Id. at 8:14–51. As shown in the table above, a patient is to receive a daily dose of PL (pyridoxal, the preferred form of vitamin B6); folate; and vitamin B12. *Id*. at 6:12–17, 8:14–51.

Example 1 of EP 005 reports that a successful treatment is considered to be a reduction in homocysteine plasma levels below 16.3µmol/l. *Id.* at 13:28–30. Example 8 reports the administration of vitamins B6 and B12, as well as folate, to patients with hyperhomocysteinemia. *Id.* at 17:25–27. EP 005 defines "elevated plasma homocysteine" as greater than 16.3µmol/l. *Id.* at 17:28.

d. Niyikiza II (Ex. 2015)

Niyikiza II, a meeting abstract, considers the relationship of metabolite profile in relation to the toxicity of pemetrexed. Ex. 2015, 558a, Abstract 2139. Specifically, Niyikiza II teaches that of 246 patients being treated with pemetrexed in Phase II trials, 118 also had the vitamin metabolites homocysteine, cystathionine, and methylmalonic acid measured

at baseline and once each cycle thereafter. *Id.* Niyikiza II performed a statistical analysis to determine which among a set of prespecified predictors, including vitamin metabolites, might correlate with toxicity. *Id.* Niyikiza II found a strong correlation between baseline homocysteine levels and the development of certain toxicities, with toxicity being seen in all patients with homocysteine levels over 10 μM. *Id.* Niyikiza II, however, found no correlation between toxicity and the remaining prespecified predictors. *Id.* Furthermore, according to Niyikiza II, "[m]aximum homocysteine levels did not appear to change from baseline during treatment with [pemetrexed]." *Id.*

e. Calvert 1999 (Ex. 1014)

Calvert 1999 provides an overview of folate metabolism and describes features relevant to the action and toxicities of antifolate cancer agents. Ex. 1014, 3. According to Calvert 1999, the development of cancer therapeutics has been linked intimately to the study of folic acid metabolism and the action of antifolate drugs. *Id*. Calvert 1999 depicts the chemical structures of various antifolates, including methotrexate, lometrexol and MTA. *Id*. at 6. Folic acid supplementation is said to reduce the toxicity of antifolate drugs. *Id*. at 8. Calvert 1999 also discusses, however, how it had been difficult to correlate antifolate-induced toxicity with pretreatment folate levels. *Id*.

Calvert 1999 teaches that intracellular homocysteine can be reduced by converting it to methionine through remethylation by methionine synthase. *Id*. at 8–9; Pet. 17. Figure 8 of Calvert 1999 is reproduced below:

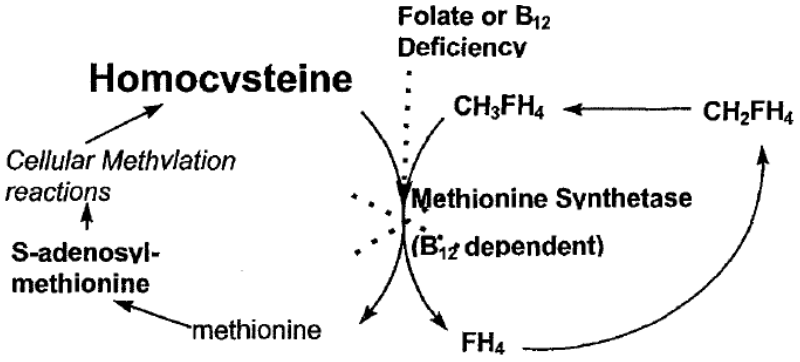


Fig 8. Role of 5-methyl tetrahydrofolic acid: a reduction in functional folate increases plasma homocysteine levels.

Id. at 9. As depicted in Figure 8 of Calvert 1999, methionine synthase requires folate (5-methyltetrahydrofolate) as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction. According to Calvert 1999, an increase in the plasma level of homocysteine occurs when there is a functional deficiency in either B12 or folate, and that the "measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA." *Id.* at 8–9.

f. Carrasco[14] (Ex. 1020)

Carrasco teaches that deficiencies of vitamin B12 and folic acid lead to megaloblastic anemia ("MA"), as well as induce increases in the levels of methylmalonic acid and homocysteine. Ex. 1020, 767. A presentation of MA may be acute megaloblastosis ("AM"). *Id.* According to Carrasco, in vitamin B12 deficiencies both homocysteine ("HCY") and methylmalonic acid ("MMA") levels are high, whereas in folate deficiencies, only homocysteine levels are increased. *Id.* at 768.

Carrasco states:

> A 45-year old male was diagnosed as having Philadelphia-positive chronic myelogenous leukemia. Three

[14] Marina Carrasco et al., *Acute Megaloblastic Anemia: Homocysteine Levels Are Useful for Diagnosis and Follow-Up*, 84 HAEMATOLOGICA 767 (1999) (Ex. 1020) ("Carrasco").

> years after diagnosis the patient developed a lymphoid blast crisis and was started on a chemotherapy protocol. The first consolidation treatment consisted of 6-mercaptopurine, methotrexate (MTX), VM-26 and cytarabine. MTX rescue with folinic acid was performed following standard guidelines. On day +14 a platelet count of $9x10^9$/L was found. Hb was 99 g/L, mean corpuscular volume (MCV) 92 fL and leukocyte count was $7.06x10^9$/L with 84% of neutrophils with hypersegmentation. Reticulocyte count was $0.053x10^{12}$/L (1.66%). Vitamin B_{12} levels and red cell folate were 322 pmol/L (normal 150-1200) and 938 nmol/L (normal 441-1285), respectively. A BM aspirate revealed 30% of erythroid precursors with megaloblastic features and a 55% of myeloid precursors with increased size and no blast cells. Serum HCY levels were 38 μmol/L (normal < 16). The patient was diagnosed as having AM and began treatment with folinic acid 12 mg iv in one single dose and folic acid 5 mg/day po for 14 days and parenteral vitamin B_{12} 2 mg/day for 4 consecutive days. After 10 days of treatment the platelet count increased to $112x10^9$/L and reticulocyte count to $0.163x10^{12}$/L (5.41%). Vitamin B_{12} level was 716 pmol/L, red cell folate level 1,506 nmol/L and serum HCY level decreased to normal value (9 μmol/L) . . . .

Id. at 767–68.

g. Hammond I (Ex. 1022)

Hammond I, a meeting abstract, teaches that MTA displays broad antitumor activity, but that "[m]yelosuppression precluded dose escalation above 500–600 mg/m^2." Ex. 1022, 129, Abstract 620P. Hammond I notes that as preclinical evaluations have indicated that folic acid supplementation increases the therapeutic index of pemetrexed, the authors undertook the study to determine if supplementation with folic acid "permits significant dose-escalation above the recommended phase II dose of [pemetrexed] alone." *Id.* The authors measured vitamin metabolites to determine their value as prognostic indicators. *Id.*

In the method, 33 patients were given 90 courses of folic acid at 5 mg/day, for 5 days, starting 2 days before pemetrexed was given at 600, 700, 800, and 925 mg/m^2. *Id.* In addition, vitamin metabolites were measured during the first two cycles as potential determinants of principal toxicities and effects. *Id.*

The authors conclude that the addition of folic acid "may reduce the usefulness of vitamin metabolites as predictors of toxicity." *Id.* The authors conclude further that folic acid supplementation "appears to permit MTA dose escalation by ameliorating toxicity." *Id.*

h. Hammond II[15] (Ex. 2035)

Hammond II, another meeting abstract, considers the feasibility of administering 5 mg of folic acid for 5 days, starting 2 days before treatment with pemetrexed, to patients. Ex. 2035, 225a, Abstract 866. According to Hammond II, serum folic acid levels do not appear to be related to pemetrexed toxicity, but notes that "homocysteine was significantly elevated in the [patient] with severe toxicities at the 800 mg/m^2 dose." *Id.* Hammond II concludes that "folic acid supplementation appears to permit [pemetrexed] dose escalation." *Id.*

i. Rinaldi (Ex. 2022)

Rinaldi, a meeting abstract, describes administering escalating doses of pemetrexed intravenously every 21 days to patients with refractory, solid tumors in order to assess toxicities and determine the maximum tolerated

[15] L. Hammond et al., *A Phase I and Pharmacokinetic (PK) Study of the Multitargeted Antifol (MTA) LY231514 with Folic Acid*, PROC. AM. SOC'Y CLINICAL ONCOLOGY, 1998, at 225a, Abstract 866 (Ex. 2035) ("Hammond II").

dose, as well as to look at its pharmacokinetic profile and potential antitumor activity. Ex. 2022, 489, Abstract 1559. Thirty-seven patients were treated with 132 courses at nine different dose levels ranging from 50 to 700 mg/m^2. *Id.* Rinaldi found the maximum tolerated dose to be 600 mg/m^2, "with reversible neutropenia, thrombocytopenia, and fatigue as the dose-limiting toxicities." *Id.* According to Rinaldi, pemetrexed "is a promising agent for the treatment of gastrointestinal malignancies." *Id.*

j Laohavinij[16] (Ex. 2031)

Laohavinij teaches that lometrexol is an antifolate that inhibits glycinamide ribonucleotide formyltransferase ("GARFT"), an enzyme required for *de novo* purine synthesis. Ex. 2031, Summary. According to Laohavinij, lometrexol has activity against tumors that are refractory to other drugs, and in particular, refractory to methotrexate. *Id.* "[I]nitial clinical development of lometrexol was curtailed because of severe and cumulative antiproliferative toxicities." *Id.* Thus, Laohavinij looked at the "effect of folic acid on lometrexol pharmacodynamics, in order to determine whether folic acid improves tolerance of lometrexol." *Id.* at 326.

Laohavinij recruited 43 patients for the study. *Id.* Patients were given daily folic acid "as a single 5 mg tablet for 7 days prior to and 7 days following lometrexol administration at 4 week intervals." *Id.* If repeated courses of lometrexol were sufficiently tolerated with an acceptable toxicity, the amount of lometrexol administered was escalated, and the interval of lometrexol administration was shortened to three weeks. *Id.* at 326–27.

[16] Sudsawat Laohavinij et al., *A Phase I Clinical Study of the Antipurine Antifolate Lometrexol (DDATHF) Given with Oral Folic Acid*, 14 INVESTIGATIONAL NEW DRUGS 325 (1996) (Ex. 2031) ("Laohavinij").

According to Laohavinij, "[t]he most important finding of this study is that 7 days of folic acid at 5 mg/day increased the plasma folate concentrations significantly and that lometrexol given with folic acid was well tolerated in most patients up to doses of at least 170 mg/m^2 every 3 weeks." *Id.* at 333. Laohavinij teaches, therefore, that a clinically acceptable schedule for the administration of a GARFT inhibitor has been identified, and that information "will facilitate the future evaluation of this class of compounds in cancer therapy." *Id.*, Summary

k. Worzalla (Ex. 1005)

Worzalla looked at the "effects of folic acid on modulating the toxicity and antitumor efficacy of LY231514," the multitargeted antifolate MTA. Ex. 1005, Abstract. Worzalla states that "[s]everal animal studies have [shown] that folic acid supplementation in combination with antifolate cancer therapy can prevent delayed toxicity and enhance the therapeutic potential." *Id.* at 3235. The lethality of MTA was compared in mice maintained on a standard diet and a low folate diet. *Id*., Abstract.

According to Worzalla, "[d]ietary folate deprivation has previously been shown to markedly enhance the toxicity of lometrexol," another antifolate. *Id.* at 3236. In order to determine the effect of folate in the diet on the toxicity of MTA, Worzalla determined LD_{50} (the amount that will kill half of the test animals) values in mice maintained on a standard diet or a low folate diet. *Id.* Worzalla reports that the dosage of folic acid ingested for standard diet mice was about 1 to 2 mg/kg/day and 0.001 to 0.008 mg/kg/day for the low folate diet mice. *Id*.

Table II of Worzalla reports the results of the treatment and shows that MTA-treated mice fed a standard diet demonstrated 100% tumor

inhibition at a dose of 30 mg/kg/day with 11 of 14 mice tumor-free on day 100 after tumor implantation. *Id*. at 3237–38. Worzalla concludes that "[f]olic acid supplementation was demonstrated to preserve the antitumor activity of [MTA] while reducing toxicity." *Id.*, Abstract. Worzalla states that the combination of MTA and folic acid may provide a mechanism for enhanced clinical antitumor selectivity. *Id*.

l. Zervos[17] (Ex. 1016)

Zervos teaches that "[s]tudies in animal models and humans have revealed that folate nutritional status may be correlated with toxicity and antitumor activity of antifolates." Ex. 1016, 256a, Abstract 907. Thus, Zervos teaches that supplementation with folic acid may play a role in protecting against toxicities that are seen with antifolate drugs. *Id.* Zervos assessed functional folate status by looking at serum concentrations of homocysteine, cystathione, and methylmalonic acid. *Id.* According to Zervos, eight patients that were found to be folate deficient had elevated levels of homocysteine and cystathione, but normal levels of methylmalonic acid. *Id.*

m. Rusthoven[18] (Ex. 1011)

Rusthoven describes a Phase II study evaluating the efficacy and safety of multitargeted antifolate LY231514 ("MTA") in patients receiving

[17] Peter H. Zervos et al., *Functional Folate Status As a Prognostic Indicator of Toxicity in Clinical Trials of the Multitargeted Antifolate LY231514*, 16 PROC. AM. SOC'Y CLINICAL ONCOLOGY, 1997, at 256a, Abstract 907 (Ex. 1016) ("Zervos").

[18] James J. Rusthoven et al., *Multitargeted Antifolate LY231514 As First-Line Chemotherapy for Patients with Advanced Non-Small-Cell Lung Cancer: A Phase II Study*, 17 J. CLIN.-ICAL ONCOLOGY 1194 (1999) (Ex. 1011) ("Rusthoven").

initial chemotherapy for advanced non-small-cell lung cancer ("NSCLC"). Ex. 1011, Abstract. The study involved thirty-three patients, all of whom were assessed for toxicity. *Id*. Initial MTA dosages were reduced after three patients received MTA treatment because of toxicity seen in the study and another Canadian MTA trial in colorectal cancer. *Id*. Rusthoven states that earlier MTA studies suggested that "dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice." *Id*. at 1195.

Based on the results of the study, Rusthoven reported that MTA seems to have exhibited a clinically meaningful activity against NSCLC and toxicity was said to be "generally mild and tolerable," although ten of the thirty-three patients stopped the protocol therapy due to toxicity. *Id*. at Abstract. Rusthoven states that their group is conducting a Phase II study of MTA in combination with cisplatin drugs for NSCLC. *Id*. at 1198.

ii. Analysis

a. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness,

i.e., secondary considerations. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

Secondary considerations may include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406; *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1358–59 (Fed. Cir. 2013). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness" and "enable[ ] the court to avert the trap of hindsight." *Leo Pharm. Prods.* 726 F.3d at 1358 (first alteration in original) (internal quotation marks and citations omitted). "This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citations omitted).

The obviousness analysis requires that "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success," even "[i]f all elements of the claims are found in a combination of prior art references." *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). We analyze the asserted ground of unpatentability in accordance with the above-stated principles.

b. Background

Cancer cells, because they are actively dividing, require large quantities of DNA and RNA. Pet. 16. The folate pathway is involved in the synthesis of DNA and RNA precursors, and, interfering with that synthesis

causes cell death or stasis. *Id.* at 15–16. Antifolates inhibit one or more enzymes in the folate pathway by binding to them in place of folate. PO Resp. 5. Antifolates, however, exert their effects on all proliferating cells, not just cancer cells, and can cause severe side effects (i.e., toxicities). Pet. 16. According to Petitioner, it was well known in the art that antifolates, such as MTA (i.e., pemetrexed) and methotrexate, had anticancer properties, and that it was known that toxicity had limited the administration of antifolates. Pet. 15–16.

According to Petitioner, by June of 1999, "extensive research into antifolate toxicity indicated that elevated levels of blood homocysteine were observed in patients treated with antifolate, such as pemetrexed." *Id.* (citing Ex. 1001, 2:14–26; Ex. 1014, 8–9; Ex. 1016, 256a, Abstract 907). Those studies, Petitioner asserts, "showed that folic acid supplementation reduced antifolate toxicity by lowering elevated homocysteine levels." *Id.* at 16–17 (citing Ex. 1010, 4; Ex. 1016, 256a, Abstract 907).

Petitioner asserts further that it was also known prior to June of 1999 that "antifolate also raised methylmalonic acid [("MMA")] levels along with homocysteine levels." *Id.* at 17 (citing Ex. 1025 ¶ 78). In addition, Petitioner argues, it was also well known that elevated MMA was linked to vitamin B12, also known as cobalamin, deficiency. *Id.* Specifically, Petitioner argues that there are only two enzymes that require vitamin B12: methionine synthase and methylmalonyl CoA mutase, and when the enzymatic reactions those enzymes catalyze are impaired, both MMA and homocysteine accumulate. *Id.* at 17–18 (citing Ex. 1012, 411; Ex. 1017, 92; Ex. 1018, 239). It was also well known, Petitioner contends, that homocysteine and MMA levels needed to be monitored in patients being

treated with antifolate. *Id.* at 18 (citing Ex. 1008, 126–27, Abstract 609P; Ex. 1017, 93).

c. Petitioner's Challenge

We start our analysis with independent claim 1, and note that the same analysis applies equally to independent claim 12, the only other independent claim challenged in this case. Claim 1 is drawn to a method of administering pemetrexed disodium, wherein an effective amount of folic acid and an effective amount of an MMA lowering agent, such as vitamin B12, is administered before the administration of pemetrexed disodium. Ex. 1001, 10:56–65.

Petitioner relies on Niyikiza for teaching administering an effective amount of pemetrexed disodium. Pet. 26. Petitioner relies upon Niyikiza also for teaching one of ordinary skill in the art that MTA has activity in a variety of tumors and that toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. *Id*. at 26–27 (citing Ex. 1008, 126–27, Abstract 609P). Petitioner explains that it was known in the art that homocysteine could be reduced by two pathways, including remethylation by methionine synthase, which requires folate as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction. *Id*. at 17 (citing Ex. 1012, 411; Ex. 1014, 8–9). Thus, Petitioner contends, Niyikiza's disclosure that "MTA-induced elevated levels of homocysteine following MTA treatment cause severe toxicities" would lead the ordinary artisan to look for ways to lower those levels, such as those taught by the '974 patent and EP 005. *Id.* at 27 (citing Ex. 1025 ¶ 114; Ex. 1001, 2:29–31).

Petitioner relies on the '974 patent and EP 005 for teaching "administering an effective amount of folic acid" in order to "reduce antifolate toxicity caused by elevated plasma homocysteine levels." *Id.* at 27–28 (citing Ex. 1001, 10:57–58; Ex. 1009, 1:46–53; 1010, 19). Thus, Petitioner asserts, the ordinary artisan would have administered folic acid to a patient in order to ameliorate the toxic effects of pemetrexed. *Id.* at 28–29 (citing Ex. 1025 ¶¶ 114, 118–119).

Petitioner asserts that Niyikiza teaches that MMA and homocysteine levels should be measured in cancer patients at the beginning and during treatment with pemetrexed to assess the toxicity of the drug, and, therefore, the ordinary artisan would have administered a methylmalonic acid lowering agent "in order to lower MMA levels, elevated homocysteine levels, and to reduce pemetrexed toxicity." *Id.* at 28–29 (citing Ex. 1025 ¶¶ 120–121). Petitioner argues that the ordinary artisan would have understood that vitamin B12 would lower MMA levels, and also would have understood from EP 005 that vitamin B12 in combination with folic acid would have reduced homocysteine levels and, in fact, that an unexpected synergism would have been seen when vitamin B12 and folate were given concurrently. *Id.* at 29 (citing Ex. 1025 ¶ 121; Ex. 1010, 2, 11).

Petitioner contends that the ordinary artisan would have understood that vitamin B12 should be administered with folic acid in order to reduce homocysteine levels, as the remethylation of homocysteine to methionine requires both folic acid and a MMA lowering agent, such as vitamin B12. *Id.* (citing Ex. 1025 ¶¶ 121, 124, 86–87, 178; Ex. 1010, 2). Petitioner relies

on Refsum[19] and Allen[20] for support. *Id.* at 29–30. In particular, Petitioner notes that Refsum discloses that measurement of homocysteine is a "promising laboratory test for evaluating cobalamin or folate deficiency status," and that its measurement may be particularly useful when used in conjunction with MMA, a "specific measure of disturbances of cobalamin metabolism." *Id.* at 30 (quoting Ex. 1012, 411–12) (citing Ex. 1025 ¶ 125). Petitioner asserts, therefore, that the ordinary artisan would have understood that administering folic acid alone would have resulted in a deficiency of vitamin B12 "because remethylation of homocysteine requires both folic acid and vitamin B12, and that vitamin B12 deficiency would raise methylmalonic acid levels." *Id.* at 30 (citing Ex. 1025 ¶ 127). The ordinary artisan, thus, would have administered an MMA lowering agent such as vitamin B12, Petitioner asserts, in order to ameliorate pemetrexed toxicity. *Id.*

d. Pretreatment with Folic Acid

As noted above, independent claim 1 recites "administering an effective amount of folic acid . . . followed by administering an effective amount of pemetrexed disodium." Ex. 1001, 10:56-64. Independent claim 12 has a similar requirement of pretreating a patient with folic acid before administering pemetrexed disodium. Id. at 11:26-12:4.

[19] Helga Refsum & Per Magne Ueland, *Clinical Significance of Pharmacological Modulation of Homocysteine Metabolism*, 11 TIPS REVIEWS 411 (1990) ("Refsum") (Ex. 1012).

[20] Robert H. Allen et al., *Diagnosis of Cobalamin Deficiency I: Usefulness of Serum Methylmalonic Acid and Total Homocysteine Concentrations*, 34 AM. J. HEMATOLOGY 90 (1990) ("Allen") (Ex. 1017).

Initially, we note that Petitioner, in its Reply, argues that Patent Owner's expert, Dr. Chabner, did not provide his opinions from the perspective of a person of ordinary skill in the art, and, thus, we should give his opinions little, if any weight. Reply 2–3. We take Petitioner's arguments into consideration as we consider Dr. Chabner's opinions herein, and give them the appropriate weight.

Patent Owner responds that it was well known as of June 1999 that "because antifolates operate by competing with folates to bind to specific enzymes, administering folates would counteract the activity of antifolates." PO Resp. 6 (citing Ex. 2120 ¶¶ 62–65; Ex. 2118 ¶¶ 46, 57; Ex. 2040, 6122). That is, according to Patent Owner, the ordinary artisan "would have understood that pemetrexed's efficacy against cancer arises from the same mechanism as its undesirable toxicities." *Id.* at 19 (citing Ex. 2120 ¶¶ 43, 49, 62–63; Ex. 2118 ¶¶ 48–49). Thus, Patent Owner argues, the ordinary artisan would have expected that administering a folate along with an antifolate "would have decreased the beneficial anti-proliferative effect of the antifolate." *Id.* at 6. Patent Owner further asserts that Petitioner's expert, Dr. Bleyer, acknowledged during his deposition that the ordinary artisan would balance reducing efficacy with reducing toxicity. *Id.* at 18 (citing Ex. 2028, 311).

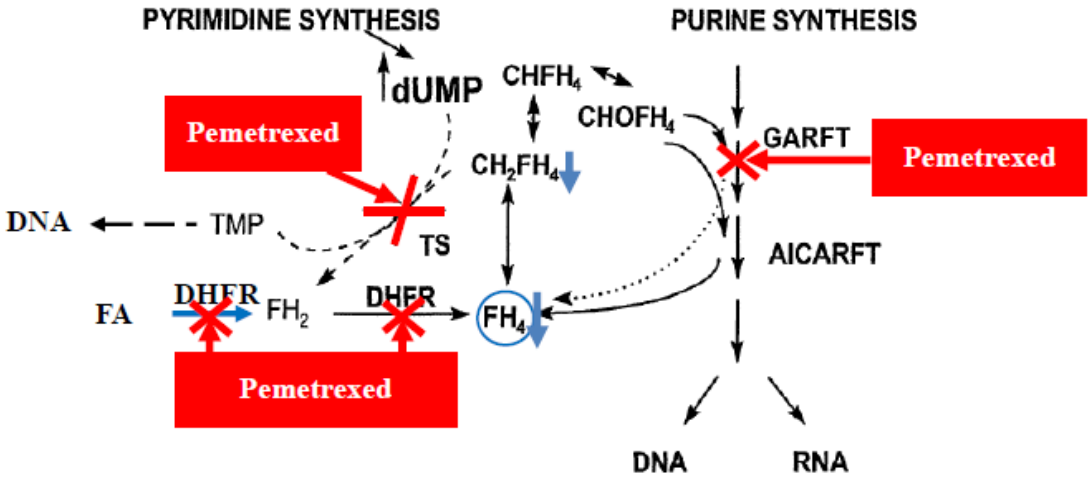
Patent Owner cites the entry for methotrexate in the 1999 *Physician's Desk Reference*, which states that "[v]itamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate." *Id.* at 19 (quoting Ex. 2020, 1398) (citing Ex. 2025, 1282; Ex. 2120 ¶ 64). Patent Owner asserts also that the labeling accompanying the antifolate raltitrexed states: "[F]olinic acid, folic acid, or vitamin

preparations containing these agents *must not be given* immediately prior to or during administration of Tomudex, since they may interfere with its action." *Id.* (quoting Ex. 2021, 1544; Ex. 2120 ¶ 65).

Moreover, Patent Owner contends that the ordinary artisan would have been concerned that pretreatment with folic acid may in fact enhance the growth of the patient's cancer. *Id.* at 20 (citing Ex. 2120 ¶¶ 33a, 61, 66–67, 166). In fact, according to Patent Owner, antifolate chemotherapy got its start in the 1940s when Dr. Sidney Farber "observed that when children with acute leukemia were given injections of folic acid conjugates, the growth of the children's tumors accelerated." *Id.* (citing Ex. 2042, 787; Ex. 2120 ¶¶ 66, 198–200 (explaining that Dr. Farber's findings are not limited to patients with acute lymphoblastic leukemia and would apply to other types of cancers); Ex. 2118 ¶ 46; Ex. 2031, 333 & n.35 (citing Farber's work)). Patent Owner argues, therefore, that the primary purpose of administering pemetrexed is the treatment of cancer, and "folic acid and vitamin B_{12} pretreatment would have been understood to frustrate that central goal." *Id.* at 29 (citing Ex. 2120 ¶ 91).

In its Reply, Petitioner argues that the ordinary artisan would have understood that folic acid is not an "antidote" for pemetrexed. Reply 12–14. According to Petitioner, the action of pemetrexed, in part, is due to its decreasing the amount of tetrahydrofolate available for DNA synthesis. *Id.* at 12 (citing Ex. 1077 ¶ 19; Ex. 1078 ¶ 46). Petitioner explains that folic acid is converted to tetrahydrofolate through the action of dihydrofolate reductase. *Id.* at 12–13 (citing Ex. 2118 ¶ 23). Petitioner asserts that the ordinary artisan would have understood that pemetrexed is a potent inhibitor of dihydrofolate reductase, but would have also understood that folic acid is

a poor substrate to that enzyme. *Id.* at 13 (Ex. 2078, 142; Ex. 2107, 11[21]; Ex. 1077 ¶ 19; Ex. 1078 ¶¶ 40–45).



Id. (citing Ex. 1077 ¶ 19). As shown in the figure, folic acid cannot reduce to tetrahydrofolate in the presence of pemetrexed. According to Petitioner's expert, Dr. Bleyer, the figure demonstrates that folic acid (FA in the diagram) is not in a reduced form that may be used by the body. Ex. 1077 ¶ 19. In order to become usable, Dr. Bleyer asserts, the folic acid must be reduced twice to tetrahydrofolate (FH_4 in the diagram). *Id.* According to Petitioner, leucovorin (folinic acid), one of the rescue therapies referenced by Patent Owner, is already in reduced form and does not need dihydrofolate reductase to increase the amount of tetrahydrofolate in the body, and, therefore, has a different effect than folic acid. Reply 13 (citing Ex. 1077 ¶ 20; Ex. 1078 ¶ 46; Ex. 2107, 11).

According to Petitioner, Patent Owner argues that if the inhibition of dihydrofolate reductase is sufficiently complete so that folic acid could not be converted to a usable form, it would not have a beneficial effect on

[21] The page numbering as to this exhibit refers to the page numbers added by Patent Owner.

pemetrexed toxicity. *Id.* at 13–14. Petitioner responds that it is the patient's *pretreatment* levels of homocysteine and nutritional status that predict toxicity, and the ordinary artisan, therefore, would have expected pretreating with folic acid to have a beneficial effect on toxicity prior to pemetrexed administration, that is, before the pemetrexed has an opportunity to inhibit dihydrofolate reductase. *Id.* at 13–14 (citing PO Resp. 24; Ex. 1008, 126–27, Abstract 609P; Ex. 1077 ¶ 22; Ex. 1063, 1276S; Ex. 2107, 15).

Petitioner asserts further that Patent Owner's argument that if folic acid is given before treatment with pemetrexed it will undermine the efficacy of the antifolate is erroneous. In that regard, Petitioner asserts that any reduced folates remaining would be insufficient to compete with pemetrexed, and that a single dose of folic acid as encompassed by the challenged claims encompasses the normal dietary levels of folic acid. *Id.* at 14 (citing PO Resp. 24–25; Ex. 1077 ¶¶ 23, 50; Ex. 2120 ¶ 164; Ex. 1078 ¶ 83). Petitioner asserts also that the ordinary artisan would in fact have expected that pretreatment with pemetrexed would improve the therapeutic index of pemetrexed. *Id.* at 14–16. Specifically, Petitioner argues that supplementing with folic acid increases the therapeutic index of pemetrexed, thus, allowing dose escalation of the drug. *Id.* at 14–15 (citing Ex. 1022, 129, Abstract 620P; Ex. 1011, 1195; Ex. 1005, 3237–39, Ex. 1014, 7; Ex. 1016, 256a, Abstract 907; Ex. 2035, 225a, Abstract 866; Ex. 1077 ¶ 24).

Petitioner contends in addition that contrary to Patent Owner's assertions that folic acid would feed the tumor and cause it to grow based on

the research of Dr. Farber,[22] the ordinary artisan would understand that supplementing with folic acid does not cause tumor growth. *Id.* at 17–18. In fact, Petitioner asserts "cancer growth has never been reported to be caused by folic acid supplementation in conjunction with *any* antifolate." *Id.* at 17 (citing Ex. 1077 ¶ 29; Ex. 1005; Ex. 1022, 129, Abstract 620P; Ex. 1011; Ex. 1020; Ex. 2031).

After carefully considering Petitioner's and Patent Owner's arguments and evidence, as discussed above and for the reasons set forth below, we determine that the preponderance of the evidence of record supports that it would have been obvious to the ordinary artisan at the time of invention to pretreat with folic acid before administration of pemetrexed disodium. That is, we conclude that the preponderance of evidence of record supports the finding that pretreatment with folic acid before administration of pemetrexed was taught in the prior art, and would have been known to the ordinary artisan at the time of invention.

In that regard, the '974 patent, which Petitioner relied upon in its challenge, describes the administration of folic acid to a patient before the administration of an antifolate. Ex. 1009, Abstract, 1:54–58, 2:60–3:22. In addition, other prior art submitted by Petitioner as demonstrating pretreatment with folic acid (*see, e.g.*, Reply 10, Sur-Reply 3), such as Worzalla, teach that supplementation with folic acid preserved the antitumor activity of MTA, that is, pemetrexed, while reducing its toxicity. Ex. 1005, Abstract. Hammond I teaches folic acid supplementation before the

[22] Sidney Farber et al., *Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Aminopteroyl-Glutamic Acid (Aminopterin)*, 238 NEW ENG. J. MED. 787 (1948) (Ex. 2042) ("Farber").

administration of MTA appears to permit dose escalation of the MTA by ameliorating toxicity (Ex. 1022), and Hammond II also teaches that folic acid supplementation appears to permit pemetrexed dose elevation (Ex. 2035). *See, e.g.*, PO Resp. 4, 26; Reply 9. Laohavinij, relied upon by Patent Owner, also teaches pretreatment with folic acid before the administration of the antifolate lometrexol. Ex. 2031, Abstract, 330, 333.

Patent Owner is, in essence, contending that we should discount those references, arguing that because of the mechanism of action of antifolate, as well as the work of Farber and Laohavinij, the ordinary artisan would have expected folate to be an "antidote" to the antifolate, and may also even encourage tumor growth. We decline to do so.

Obviousness is determined from the context of a person of ordinary skill in the art at the time the invention was made. "[T]he level of skill in the art is a prism or lens through which a judge, jury, or the Board views the prior art and the claimed invention. This reference point prevents these factfinders from using their own insight or, worse yet, hindsight, to gauge obviousness." *Okajima*, 261 F.3d at 1355. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *GPAC*, 57 F.3d at 1581 (internal quotations omitted).

The references discussed above, for example, the '974 patent and Hammond I and Hammond II (collectively, "Hammond" or "the Hammond Abstracts"), that suggest pretreatment with folic acid before administration of an antifolate, such as MTA, are addressing the toxicity associated with the administration of the antifolate, and balancing it with the efficacy of the

antifolate. In that regard, we credit the testimony of Petitioner's expert, Dr. Bleyer, who declares:

> In fact, despite being aware of the Farber studies, the express purpose of the Laohavinij investigators was a study of folic acid combined with an antifolate: "The objective of the present clinical study was to identify a safe dose of lometrexol when given with folate supplementation so as to allow Phase II trials, in an attempt to reproduce the efficacy of lometrexol seen in folate-deficient mice receiving folate supplementation." (Ex. 2031 at 330.) Further, after undertaking their study, the Laohavinij investigators did not warn against tumor proliferation when combining folic acid with an antifolate, but instead stated that "[t]he work described in this report has demonstrated that lometrexol toxicity can be modulated by folic acid supplementation in patients," and encouraged others to use "the information obtained from this study [to] facilitate the future development and evaluation of this class of compounds [antifolates] in the treatment of human cancer." (Ex. 2031 at 330-31.) By 1996, Laohavinij et al recommended folic acid pretreatment with lometrexol. Thus, like the Laohavinij investigators, not only was a POSA in 1999 undeterred by the 1947 Farber study from using folic acid to mediate the toxicity of antifolates, but actively considering it as a promising method for managing toxicity.

Ex. 1077 ¶ 31 (alterations in original).

In view of the multiple teachings found in the prior art that pretreatment with folic acid before administration of an antifolate helps ameliorate the toxicity of the antifolate, we find that at the time of invention, the ordinary artisan would have had a reason to pretreat with folic acid before the administration of pemetrexed sodium. "The fact that the motivating benefit comes at the expense of another benefit . . . should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be

weighed against one another." *Medichem S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 n.8 (Fed. Cir. 2000)).

Moreover, although Patent Owner argues that folic acid pretreatment would have been expected to lower or reduce pemetrexed's efficacy (PO Resp. 18–29), Patent Owner's counsel acknowledged that folic acid pretreatment would not completely eliminate pemetrexed's effectiveness (Tr. 78:15–80:6). Also, as Dr. Bleyer testifies, the ordinary artisan "would have understood that decreasing a drug's toxicity can allow a patient to receive higher/more doses of the drug, which can improve the drug's overall response, even if the toxicity reduction results in a lower efficacy per mg of drug administered." Ex. 1077 ¶ 24.

We also have carefully considered, but are not persuaded by, Patent Owner's arguments regarding Farber (Ex. 2042). Farber's seminal work was published in 1948. The references discussed here that teach pretreating with folic acid before administration of an antifolate were all published well after the date of Dr. Farber's work, and their authors would have presumably been aware of it. *See, e.g.*, *GPAC*, 57 F.3d at 1579 (noting that the person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention). And as noted by Patent Owner (PO Resp. 20), Laohavinij specifically cites Farber's work. Ex. 2031, 333 & n.35 (citing Farber's work). As Dr. Bleyer testifies, Laohavinij expressly considered the concerns identified in Farber, yet still actively considered the use of folic acid as a promising method for managing the toxicity of antifolates. Ex. 1077 ¶ 31.

Patent Owner argues that at the time of invention, "pemetrexed was recognized as a promising drug in clinical trials without any vitamin supplementation at all." PO Resp. 27 (citing Ex. 2120 ¶¶ 51–54). In fact, according to Patent Owner, at the time of invention the general understanding was that the toxicities associated with the administration of pemetrexed were understood to be manageable by conventional means. Thus, according to Patent Owner, the ordinary artisan would not have looked at means of managing those toxicities, such as through the pretreatment with vitamin B12, that could potentially have a large and unpredictable effect on the efficacy of the antifolate. *Id.* at 18–19 (citing Ex. 2120 ¶¶ 53–54, 59, 61, 86–89). Patent Owner argues further that even if the ordinary artisan had wanted to address pemetrexed toxicities, there were other, known ways to do so that would not have compromised the efficacy of the pemetrexed, such as by adjusting the dosing schedule or the use of rescue therapy. *Id.* at 27–29 (citing Ex. 2120 ¶¶ 53–61, 63, 66–67, 151; Ex. 1011, 1198; Ex. 2035, 225a, Abstract 868; Ex. 2028, 321–24).

Petitioner responds in its Reply that the ordinary artisan, in view of the prior art of record, would have had a reason to address pemetrexed's known toxicities. Reply 11–12. Petitioner relies on Calvert 1998[23] and Hammond I as teaching that those toxicities were serious. *Id.* at 11 (citing Ex. 1013, 38–39; Ex. 1022, 129, Abstract 620P). In addition, Petitioner

[23] A. H. Calvert and J. M. Walling, *Clinical Studies with MTA,* 78 (Sup. 3) BR. J. CANCER 35–40 (1998) (Ex. 1013) ("Calvert 1998).

argues, Rinaldi II[24] taught that three patients died (8%), Thödtmann[25] taught two patients died (4%), and Rusthoven taught that 30% of patients had to stop treatment because of toxicity, despite schedule modifications. *Id.* at 11–12 (citing Ex. 2030, 86; Ex. 1021, 129, Abstract 618P; Ex. 1011, 1195, 1198). Thus, given pemetrexed's promising anti-tumor activity, Petitioner asserts that the ordinary artisan would have had a reason to address its toxicity so that more patients could tolerate treatment. *Id.* at 12.

Again, we do not find Patent Owner's arguments and evidence to be persuasive. "[I]n a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (second alteration in original). Thus, the fact that there were other ways to address the toxicity of pemetrexed is not evidence that pretreatment with folic acid before administration of pemetrexed would not have been obvious to the ordinary artisan. And as noted above, each of the '974 patent, Worzalla, Hammond I, Hammond II, and Laohavinij evidence that pretreatment with an antifolate was a known way to reduce the toxicity associated with the administration of pemetrexed.

Patent Owner asserts also that the '974 patent does not help Petitioner. PO Resp. 43–44. According to Patent Owner, "[t]he '974 patent describes

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[24] David A. Rinaldi, *Overview of Phase I Trials of Multitargeted Antifolate*, SEMINARS ONCOLOGY, Apr. 1999, at 82 (Ex. 2030) ("Rinaldi II").

[25] R. Thödtmann et al., *Phase I Study of Different Sequences of MTA (LY231514) in Combination with Cisplatin in Patients with Solid Tumours*, 9 ANNALS ONCOLOGY 129, Abstract 618P (Supp. 4 1998) ("Thödtmann") (Ex. 1021).

the administration of folic acid with the antifolate lometrexol to a single cancer patient, with precious little detail." *Id.* at 43 (citing Ex. 1009, 8:52–58). Moreover, at the time of invention, lometrexol had failed clinically, even with adding folic acid. *Id.* (citing Ex. 2120 ¶ 166). Patent Owner cites Laohavinij as evidence that "the administration of folic acid prior to lometrexol and during treatment could potentially supplement the folate requirement of the tumor and thereby circumvent the activity of lometrexol, or worse still, aid tumor progression." *Id.* (quoting Ex. 2031, 333). Thus, Patent Owner asserts, the '974 patent would not provide a reason to the ordinary artisan to pretreat with folic acid when administering pemetrexed. *Id.* at 44 (citing Ex. 2120 ¶ 163).

Again, Patent Owner's argument does not persuade us that the ordinary artisan would not have administered folic acid before administration of pemetrexed sodium. Patent Owner essentially argues that the disclosure in the '974 patent does not enable one of ordinary skill in the art how to make or use the invention described therein. A U.S. patent, however, is presumed to be enabled. *Regeneron Pharm., Inc. v. Merus N.V.*, 864 F.3d 1343, 1368 (Fed. Cir. 2017). Except for arguing that there is limited data in the '974 patent and that lometrexol failed clinically, as well as presenting declaration testimony to that effect (*see* Ex. 2120 ¶ 166), Patent Owner has not demonstrated that the disclosure in the '974 patent is not enabled.

Moreover, as noted above, it is not just the '974 patent that suggests pretreatment with folic acid before treatment with an antifolate, but it is also Worzalla, Hammond I, Hammond II, and Laohavinij. Thus, Petitioner has demonstrated by a preponderance of the evidence of record that it would

have been obvious to the ordinary artisan at the time of invention to pretreat with folic acid before administration of the antifolate pemetrexed.

Patent Owner argues that during his deposition, Petitioner's expert, Dr. Bleyer "testified that '[t]here's a missing reference'—Hammond—that 'would have been a better reference to support the conclusion.'" PO Resp. 45 (alteration in original) (quoting Ex. 2027, 99). Patent Owner asserts that Petitioner cannot now rely on Hammond to make up for deficiencies in its Petition. *Id.*

Moreover, Patent Owner asserts, Hammond confirms that pretreatment with folic acid would reduce the efficacy of the pemetrexed. *Id.* Patent Owner cites Rinaldi as describing a Phase I clinical trial that was performed before that of Hammond, in which no folic acid was administered. *Id.* at 46. According to Patent Owner:

> Rinaldi reported 4 partial responses and 6 minor responses out of 37 patients, results that reflected broad antitumor activity. Ex. 2022; Ex. 2120 ¶¶ 52, 71-74; Ex. 1013 at 36-37; Ex. 1022 at 620P.
>
> Hammond used higher doses of pemetrexed than Rinaldi but showed far fewer responses. Hammond II reported only one partial response in twenty-one patients. Ex. 2035. And Hammond I, which reported on thirty-three patients (reflecting further results of the same study), no additional responses were identified. Ex. 1022; Ex. 2120 ¶¶ 71-74, 96.
>
> Far from encouraging the [ordinary artisan] to use Hammond as a starting point for designing an improved method of administering pemetrexed, therefore, the [ordinary artisan] would have viewed Hammond as a failure. Ex. 2120 ¶¶ 33b, 75, 96.

Id. Thus, Patent Owner asserts, Hammond supports the proposition that although the administration of folic acid may increase the dose of

pemetrexed that can be administered while reducing toxicity, the therapeutic efficacy is consequently reduced. *Id.* at 46–47.

Petitioner responds, however, that the ordinary artisan would not have compared the results reported by Hammond to those reported by Rinaldi. Reply 16–17. According to Petitioner, both of those references were drawn to Phase I studies, which are "designed to establish a safe and effective dose, not measure or compare efficacy." *Id.* at 16 (citing Ex. 1076, 124:20–125:15; Ex. 1075, 172:23–25, 178:2–179:13; Ex. 2043, 274, 277; Ex. 2031, 326; Ex. 1077 ¶ 27; Ex. 1080 ¶¶ 27–28). Moreover, Petitioner asserts, neither reference discloses its testing protocol, and the treatment regimens and patient populations differ, and the ordinary artisan, therefore, would understand that it is not possible to make a meaningful comparison of the two references. *Id.* at 16–17 (citing Ex. 2022; Ex. 2035; Ex. 1077 ¶ 28; Ex. 1075, 179:3–18). Finally, Petitioner asserts that Hammond concluded, and Patent Owner agreed, that supplementing with folic acid allowed for dose escalation of pemetrexed, which the ordinary artisan "would have understood . . . to be consistent with an improvement in the therapeutic index." *Id.* at 17 (citing Ex. 2035, 225a, Abstract 866; Ex. 2103, 14; Ex. 1077 ¶ 28).

We are not persuaded by the arguments and evidence of Patent Owner. We find that Petitioner is not using the two Hammond references as part of the original challenge, but rather, it is using those abstracts as demonstrating what would have been known to the ordinary artisan at the time of invention. *See Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F. 3d 1359, 1365 (Fed. Cir. 2015) ("Art can legitimately serve to document the

knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.").

As noted above, Patent Owner argues that the ordinary artisan would have seen Hammond I and Hammond II as a failure, and would have instead followed the teachings of Rinaldi, which describes a Phase I clinical trial in which no folic acid was administered. In this regard, Patent Owner essentially argues that the Hammond Abstracts teach away from using folic acid pretreatment before the administration of pemetrexed.

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Like our appellate reviewing court, "[w]e will not read into a reference a teaching away from a process where no such language exists." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006).

Here, Hammond I specifically states that folic acid supplementation "appears to permit MTA dose escalation by ameliorating toxicity." Ex. 1022, 129, Abstract 620P. Hammond II reiterates that finding, stating that "folic acid supplementation appears to permit MTA escalation." Ex. 2035, 225a, Abstract 866. As discussed above, and as explained by Petitioner's expert, Dr. Bleyer, the ordinary artisan would have understood that there was a balancing between toxicity and efficacy. *See Medichem S.A.*, 437 F.3d at 1165. Thus, as both Hammond Abstracts teach that folic acid allowed for dose escalation of MTA, that is, pemetrexed, the ordinary artisan would have found it obvious to supplement with folic acid before

administration of the MTA in order to help ameliorate toxicity, and increase the levels of the antifolate that may be administered to treat the cancer. We note, moreover, that all that is required is a reasonable expectation of success, not absolute predictability. *See id.* at 1165 ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a *certainty* of success."); *see also Pfizer*, 480 F.3d at 1364 ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

Patent Owner argues further that Petitioner's expert, Dr. Bleyer, testified as to leucovorin, that if folinic acid, which is a folate, is given before methotrexate chemotherapy, "'it will *prevent*, not reverse, *the effect*' of the drug on '*both the healthy cells and the cancer cells,*'" and testified further that "the same mechanistic expectations that apply to methotrexate would similarly apply to pemetrexed." PO Resp. 22–23 (quoting Ex. 2028, 325) (citing Ex. 2028, 331–33; Ex. 2120 ¶¶ 33b, 62–65; Ex. 2118 ¶¶ 49–51).

Patent Owner acknowledges that Dr. Bleyer "attempted to explain why he believed that folic acid—as opposed to folinic acid—would not be expected to lead to the same reduction in efficacy." *Id.* at 23 (citing Ex. 2028, 321–30). In particular, according to Patent Owner, Dr. Bleyer explained that folic acid would not have the same effect as folinic acid because methotrexate inhibits the enzyme DHFR, which is required to convert folic acid to a useful form, and, thus, folic acid would not reverse efficacy because it would not be converted to a useful form in the presence of the antifolate. *Id.* (citing Ex. 2028, 331–32). Patent Owner contends Dr. Bleyer's reasoning is incorrect for several reasons. *Id.* at 24–27.

Patent Owner asserts that if Dr. Bleyer is correct and folic acid is not converted into a usable form in the presence of an antifolate, the ordinary artisan would not expect that pretreatment with folic acid would work to reduce the toxicity of the antifolate. *Id.* at 24 (citing Ex. 2120 ¶ 179; Ex. 2118 ¶¶ 58–59). There would, therefore, be no reason to pretreat with folic acid when administering pemetrexed. *Id.* Moreover, Patent Owner argues, Dr. Bleyer fails to explain why pretreatment with folic acid would not reduce the efficacy of pemetrexed, as, "[e]ven if pemetrexed entirely blocked the conversion of folic acid to a usable form once administered, if the folic acid is given prior to the pemetrexed as the challenged claims require, a significant quantity of folic acid would likely be converted to other usable folates prior to the administration of the pemetrexed." *Id.* at 24–25 (citing Ex. 2118 ¶ 60; Ex. 2120 ¶¶ 179, 181).

Patent Owner argues also that Dr. Bleyer's reasoning is contrary to the recommendation of the *Physician's Desk Reference*, which states that methotrexate should not be administered with folic acid, as well as the labeling for raltitrexed. *Id.* at 25–26 (citing Ex. 2020, 1398; Ex. 2025, 1282; Ex. 2120 ¶¶ 64–65; Ex. 2021, 1544). In addition, Patent Owner notes that folic acid has also been reported to reduce the efficacy of lometrexol. *Id.* at 25–26 (citing Ex. 2031, 333; Ex. 2120 ¶ 68). Thus, Patent Owner asserts, Dr. Bleyer's testimony that folic acid would not be expected to have the same effect as folinic acid is counter to the teachings of the prior art. *Id.* at 26. Patent Owner argues last that Dr. Bleyer's argument, even if valid for methotrexate, which inhibits DHFR, is not valid for pemetrexed, which inhibits a different enzyme, TS, which is not needed to convert folic acid to a usable form. *Id.* (citing Ex. 2120 ¶¶ 46, 164, 179, 181; Ex. 2054, 110).

We do not find Patent Owner's argument persuasive. The fact remains that each of the '974 patent, Worzalla, Hammond I, Hammond II, and Laohavinij teach that pretreatment with folic acid ameliorates the toxicities associated with the administration of antifolates, such as pemetrexed. Thus, Patent Owner's arguments to the contrary do not convince us that it would not have been obvious to pretreat with folic acid before administering the antifolate pemetrexed.

e. Pretreatment with Vitamin B12

Independent claim 1 further recites "administering . . . an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium." Ex. 1001, 10:56-64. Independent claim 12 has a similar requirement of pretreating a patient with vitamin B12, a methylmalonic acid lowering agent, before administering pemetrexed disodium. *Id*. at 11:26-12:4.

Petitioner argues that the challenged claims should be found to be unpatentable because Niyikiza teaches that MMA and homocysteine levels should be measured in cancer patients at the beginning and during treatment with pemetrexed to assess the toxicity of the drug. Pet. 28. Thus, according to Petitioner, the ordinary artisan would have administered a methylmalonic acid lowering agent "in order to lower MMA levels, elevated homocysteine levels, and to reduce pemetrexed toxicity." *Id.* at 29 (citing Ex. 1025 ¶¶ 120–121). In particular, Petitioner asserts that the ordinary artisan would have understood that administering folic acid alone would have resulted in a deficiency of vitamin B12 "because remethylation of homocysteine requires both folic acid and vitamin B12, *and that vitamin B12 deficiency would raise methylmalonic acid levels*." *Id.* at 30 (citing Ex. 1025 ¶ 127) (emphasis

added). The ordinary artisan, Petitioner asserts, would have, therefore, administered an MMA lowering agent, such as vitamin B12, in order to ameliorate pemetrexed toxicity. *Id.*

Patent Owner, in response, explains that homocysteine is involved in the folate pathway, and normally is constantly created and converted to methionine through at least the action of methionine synthase. PO Resp. 8 (citing Ex. 2120 ¶¶ 37, 40; Ex. 2118 ¶¶ 30, 35, 42). As such, high homocysteine levels may indicate a folic acid deficiency, a vitamin B12 deficiency, or a deficiency in both. *Id.*

Patent Owner notes that elevated levels of MMA may be indicative of a vitamin B12 deficiency, but that folic acid deficiencies do not lead to elevated MMA levels. *Id.* at 8–9 (citing Ex. 2120 ¶ 40; Ex. 2118 ¶ 43). Thus, Patent Owner asserts, "if a patient had elevated homocysteine levels but did not have elevated MMA levels, this would indicate that they ha[d] a folate deficiency but not a vitamin B_{12} deficiency." *Id.* at 9.

According to Patent Owner, Dr. Niyikiza endeavored to determine those patients that would have been most likely to develop toxicities from pemetrexed, and published his results in Niyikiza (Ex. 1008, 126–27, Abstract 609P) and Niyikiza II (Ex. 2015, 558a, Abstract 2139). *Id.* at 10. Patent Owner argues that although those "abstracts explained that there was a correlation between pemetrexed toxicity and the level of homocysteine in the patients' blood prior to pemetrexed treatment," Dr. Niyikiza, in his second abstract (Niyikiza II), "found no such correlation between pemetrexed toxicity and MMA levels." *Id.* at 10–11 (citing Ex. 2015, 558a, Abstract 2139; Ex. 2120 ¶¶ 33d, 106; Ex. 2118 ¶ 70); *see also id.* at 30–31 (same). Patent Owner argues that finding suggests that there is no

correlation between pemetrexed toxicity and the patient's vitamin B12 levels. *Id.* at 11 (citing Ex. 2120 ¶¶ 33d, 106; Ex. 2118 ¶ 70); *see also id.* at 30 (same). Thus, Patent Owner asserts, the ordinary artisan would have understood that it was not a deficiency in vitamin B12 that was the cause of the elevated homocysteine levels and, thus, the ordinary artisan would have had no reason to administer vitamin B12. *Id.* at 30. Specifically, according to Patent Owner, "Niyikiza II analyzed whether patients' MMA levels were correlated with pemetrexed toxicity, and found they were not," and, therefore, provided no reason to pretreat with vitamin B12. *Id.* at 31 (citing Ex. 2015, 558a, Abstract 2139; Ex. 1016, 256a, Abstract 907; Ex. 2120 ¶¶ 104–119; Ex. 2118 ¶ 43).

Patent Owner argues that Petitioner relies on EP 005 not only for its teaching of lowering homocysteine levels using a combination of folic acid and vitamin B12, but also for its teaching of "the use of folic acid and vitamin B_{12} administration in conjunction with methotrexate." *Id.* at 41 (citing Pet. 29). Patent Owner argues that EP 005, however, is focused on reducing the risk of cardiovascular disease associated with elevated homocysteine levels, and Petitioner's expert, Dr. Bleyer agrees, that none of the patients discussed in EP 005 is a cancer patient. *Id*. (citing Ex. 2118 ¶¶ 73–74; Ex. 2120 ¶ 134; Ex. 2027, 207). Patent Owner relies on its expert, Dr. Chabner, for its assertion that the ordinary artisan would not look to EP 005 when treating a cancer patient with an antifolate because the concern would be treating the cancer, and not the possible long-term cardiovascular effects of elevated homocysteine. *Id.* (citing Ex. 2120 ¶ 135). According to Patent Owner, EP 005 does not provide any information on how pretreatment with folic acid and vitamin B12 would impact the effects of

methotrexate on cancer, or any associated toxicities. *Id.* at 42 (citing Ex. 2120 ¶ 136). Patent Owner asserts, "[a]t most, EP 005 would be understood as a way to lower homocysteine levels *after* methotrexate chemotherapy or cancer has caused them to rise." *Id.* (citing Ex. 2120 ¶ 139). Moreover, Patent Owner asserts, the ordinary artisan would have understood that the mention of methotrexate in EP 005 is related to the treatment of rheumatoid arthritis, where an antiproliferative mechanism does not appear to be involved. *Id.* at 42–43 (citing Ex. 2120 ¶¶ 137, 202–204; Ex. 2020, 1397; Ex. 2025, 1281; Ex. 2086, 282; Ex. 2087, 969–70).

Patent Owner argues that the Petition rests on an erroneous premise: "that 'MTA-induced [*i.e.*, pemetrexed-induced] elevated levels of homocysteine following MTA treatment *cause* severe toxicities.'" *Id.* at 33 (alteration in original) (quoting Pet. 27). According to Patent Owner, nothing in Niyikiza suggests "that pemetrexed toxicities are *caused* by, as opposed to correlated with, elevated homocysteine levels." *Id*. In fact, Patent Owner asserts, Niyikiza expressly teaches that *homocysteine* and albumin levels *did not appear to change from baseline during treatment with pemetrexed*. *Id.* at 34 (citing Ex. 1008, 126–27, Abstract 609P; Ex. 2120 ¶¶ 109–110). Patent Owner argues that the ordinary artisan would read Niyikiza as teaching that although patients who have elevated homocysteine levels before treatment with pemetrexed may be at increased risk for pemetrexed associated toxicities, that correlation with pemetrexed toxicity is with the baseline levels of homocysteine (i.e., before treatment with pemetrexed). *Id.* Thus, Patent Owner asserts, Niyikiza does not suggest that the pemetrexed induces increases in homocysteine levels, or even that it is the homocysteine itself that causes the toxicities. *Id.*

Petitioner relies on EP 005, Patent Owner asserts, for its teaching "that *methotrexate* can increase homocysteine during the course of methotrexate treatment," and that EP 005 "states generally that 'folate antagonistic drugs' may do so." *Id.* at 34. According to Patent Owner, however, EP 005 nowhere mentions other antifolate drugs such as pemetrexed and, thus, there is nothing in that reference that would convince the ordinary artisan that Niyikiza's "specific observations" regarding the effect of administration of pemetrexed on homocysteine levels was incorrect. *Id.* at 34–35.

Patent Owner notes that Petitioner's expert, Dr. Bleyer, stated during a deposition that the ordinary artisan may have discounted the results presented by Niyikiza because the ordinary artisan "would have believed that Dr. Niyikiza failed to detect a 'peak' in homocysteine levels after pemetrexed administration." *Id.* at 35 (citing Ex. 2027, 63–65). Dr. Bleyer admitted, however, that he had no data to support that assertion, and the one reference Dr. Bleyer did cite, Broxson,[26] refers to the administration of methotrexate followed by administration of folate, wherein homocysteine levels rose after the administration of methotrexate, and then fell after the administration of folate. *Id.* (citing Ex. 2122; Ex. 2120 ¶ 128; Ex. 1012, 415). That is different from the protocol followed in Niyikiza, Patent Owner asserts, as the patients in Niyikiza's study did not receive folate, and, thus, Broxson would not suggest to the ordinary artisan that there may have been

[26] Emmett H. Broxson et al., *Changes in Plasma Methionine and Total Homocysteine Levels in Patients Receiving Methotrexate Infusions*, 49 CANCER RES. 5879 (1989) (Ex. 2122) ("Broxson").

a peak in the patients' homocysteine levels that Niyikiza may have missed. *Id.* (citing Ex. 2120 ¶ 128).

Patent Owner argues also that the ordinary artisan at the time of invention would also not have had any reason to treat homocysteine levels *per se*, as suggested by Petitioner. *Id.* at 35. The baseline homocysteine levels reported by Niyikiza that correlated with increased toxicities with pemetrexed treatment, were not, by themselves, abnormally high. *Id.* at 36 (citing Ex. 2118 ¶¶ 64–66; Ex. 2120 ¶ 117–118). EP 005 discloses that hyperhomocysteinemia is associated with levels of homocysteine greater than 16.3 µM, whereas Niyikiza taught that homocysteine levels of 10 µM or more correlated with increased toxicity, which the ordinary artisan in view of EP 005 would not consider to be abnormally elevated or in need of treatment. *Id.* (citing Ex. 2118 ¶ 66; Ex. 2120 ¶¶ 117–118; Ex. 1010, 13–14; Ex. 2027, 226).

Patent Owner relies also on the testimony of its expert, Dr. Chabner, as demonstrating that the toxicities associated with the administration of pemetrexed are different from those associated with hyperhomocysteinemia. *Id.* at 37. The toxicities associated with the administration of pemetrexed as reported by Niyikiza were toxicities to rapidly dividing cells, such as the bone marrow in neutropenia, whereas the toxicities associated with hyperhomocysteinemia reported by EP 005 included cardiovascular risk, arteriosclerosis, mental retardation, osteoporosis, thrombosis, and neurodegenerative pathologies. *Id.* (citing Ex. 2120 ¶¶ 109, 113; Ex. 2118 ¶ 27). In addition, Patent Owner argues that the patients in Niyikiza did not experience any toxicities until treatment with pemetrexed and, thus, the ordinary artisan would have understood that it was not the homocysteine

levels *per se* that need to be treated. *Id.* at 37–38 (citing Ex. 1008, 126–27, Abstract 609P; Ex. 1014, 9 & n.17; Ex. 2120 ¶¶ 114–116). Even if the ordinary artisan would have attempted to lower homocysteine levels, Patent Owner asserts, there were other ways to do so known to the ordinary artisan that would not risk interfering with the efficacy of the pemetrexed to treat cancer, such as the use of betaine. *Id.* at 39 (citing Ex. 2033, 2805; Ex. 2120 ¶¶ 130–132).

In addition, Patent Owner argues that contrary to Petitioner's suggestion (Pet. 19), "folic acid and vitamin B_{12} had never before been combined in a pretreatment regimen," asserting that "[v]itamin B_{12} pretreatment, in fact, was completely unprecedented in the antifolate literature." *Id.* at 38 (citing Ex. 2027, 179–83; Ex. 2120 ¶¶ 83–85; Ex. 2118 ¶ 63). According to Patent Owner, an ordinary artisan would have understood that the combination of vitamin B12 and folic acid "would have reduced the efficacy of the drug, and indeed, would have been expected to encourage the cancer's growth." *Id.* at 18 (citing Ex. 2120 ¶¶ 33b, 61–67, 87–89, 140; Ex. 2118 ¶¶ 46, 50–51).

Patent Owner argues that vitamin B12 "can also interfere with an antifolate's anti-cancer efficacy by increasing folate levels." *Id.* at 6 (citing Ex. 2120 ¶¶ 37–39; Ex. 2118 ¶ 29). Specifically, Patent Owner argues that vitamin B12 is required to convert an inactive form of folate into an active form, which active form may then be used to make DNA precursors. *Id.* at 6–7. In particular, the enzyme methionine synthase, which requires vitamin B12, converts 5-methyltetrahydrofolate ("5-MTHF"), an inactive form of folate, into tetrahydrofolate, an active form, and, at the same time, converts homocysteine to methionine. *Id.* at 7 (citing Ex. 2118 ¶¶ 30–34). Thus,

Patent Owner notes, a deficiency in vitamin B12 will lead to accumulation of 5-MTHF and homocysteine in the cell, creating a "methyl trap." *Id.* (citing Ex. 2118 ¶¶ 32, 35). That is, folate is trapped in its inactive form, 5-MTHF, leading to a reduced amount of active folate available to synthesize DNA, even though the total amount of folate may not be low. *Id.* (citing Ex. 2120 ¶ 39; Ex. 2118 ¶¶ 30–34). Adding a small amount of vitamin B12, Patent Owner argues, "has the potential to increase a patient's folate level more than just administering a folate, because administering vitamin B_{12} could convert a large pool of 'trapped' folate into its active form." *Id.* (citing Ex. 2120 ¶¶ 52–56, 123; Ex. 2118 ¶¶ 34, 53–56). Thus, Patent Owner argues that the ordinary artisan would have understood that administering vitamin B12 could release a potentially large amount of folate, which the ordinary artisan would have expected to reduce the anti-cancer properties of the antifolate. *Id.* at 8 (citing Ex. 2120 ¶¶ 33c, 39, 85–87, 102–103, 123, 206; Ex. 2118 ¶¶ 52–56).

Petitioner responds in its Reply that the ordinary artisan would have had a motivation to use pemetrexed with folic acid and vitamin B12 pretreatment with a reasonable expectation of success. Reply 18–27.

Petitioner asserts that, as acknowledged by Patent Owner, both Niyikiza Abstracts taught the ordinary artisan at the time of invention "that *pretreatment* homocysteine levels ≥10 μM strongly correlate with severe pemetrexed toxicity." *Id.* at 18 (citing PO Resp. 10–11; Ex. 1008, 126–27, Abstract 609P; Ex. 2015, 558a, Abstract 2139; Ex. 1014, 9; Ex. 1073, 71–72; Ex. 1077 ¶ 40). Moreover, Petitioner asserts, it is irrelevant whether the homocysteine is causative of the pemetrexed toxicity, because, as admitted by Dr. Zeisel, the ordinary artisan "would have known that, for some

patients, low B_{12} and/or low folate status causes elevated homocysteine which, in turn, correlates with pemetrexed toxicity." *Id.* at 19 (citing Ex. 1076, 40:10–19, 41:5–12; Ex. 1075, 280:10–20). Thus, Petitioner argues that the ordinary artisan "would have known that low B_{12} and/or low folate status could have been the reason for their pemetrexed toxicity risk." *Id.* at 19–20 (citing Ex. 1076, 41:5–12). According to Petitioner, the ordinary artisan would have known that patients with elevated homocysteine levels could be treated with some combination of four nutrients: vitamin B12, vitamin B6, folate, and betaine. *Id.* at 20 (citing Ex. 1076, 34:16–23, 139:9–14; Ex. 1049, 197; Ex. 2066, 1931; Ex. 1098, 343; Ex. 1077 ¶ 64; Ex. 1078 ¶¶ 84–87, 94). Thus, Petitioner contends, "[b]ecause the prior art showed *pretreatment* homocysteine levels correlated with pemetrexed toxicity, [the ordinary artisan] would have reasonably expected that *pretreatment* supplementation with folic acid and B_{12} would have been effective in lowering pretreatment homocysteine levels and thus reduce the risk of pemetrexed toxicity." *Id.* (citing Ex. 1077 ¶¶ 40, 47).

Petitioner asserts that the prior art taught that "supplementing a patient with both folic acid and B_{12} was significantly more efficacious than supplementing with either vitamin alone," and that was known to be true even in patients with homocysteine levels in what would be considered normal levels. *Id.* at 20–21 (citing Ex. 1077 ¶¶ 51, 53; Ex. 1063, 1277S–78S; Ex. 1099, 190; Ex. 1019, 1109; Ex. 1010, 18). Petitioner cites specifically EP 005 for its teaching that "'it is known that vitamin B_6, vitamin B_{12} and folate play a role in regulating the methionine-homocysteine pathway and controlling levels of homocysteine,' such that supplementation with these vitamins is appropriate 'in the treatment of raised homocysteine

levels induced nutritionally or . . . in combination with a B_6 or folate antagonistic drug' or in the case of 'leukemia [or] other cancers.'" *Id.* at 21 (alteration in original) (quoting Ex. 1010, 4, 9). Petitioner argues that Patent Owner's argument that EP 005 only suggests supplementation after pemetrexed treatment ignores the teaching of EP 005 that the vitamins can be administered for the prophylaxis of elevated levels of homocysteine. *Id.* at 21–22 (citing Ex. 1010, 4, 9; Ex. 1077 ¶ 51). Moreover, Petitioner argues that EP 005 "applies to 'the treatment of raised homocysteine levels induced nutritionally,' which the prior art taught is a concern for patients that have low folate and/or B_{12} levels before pemetrexed treatment." *Id.* at 22 (citing Ex. 1010, 9; Ex. 1077 ¶¶ 40, 47; Ex. 1078 ¶¶ 80–87, 91).

According to Petitioner, the ordinary artisan would have had a reasonable expectation of success that supplementing with folic acid and vitamin B12 before treatment with pemetrexed would reduce pemetrexed toxicity. *Id.* at 23–27. Petitioner asserts:

> The prior art taught that: (1) elevated *pretreatment* homocysteine correlates strongly with pemetrexed toxicity, (2) low folate and low B_{12} are each causes of elevated homocysteine (3) folic acid + B_{12} *pretreatment* synergistically reduces pretreatment homocysteine levels, (4) folic acid supplementation is effective in reducing pemetrexed toxicity; and (5) there is a correlation between reducing homocysteine levels and reducing pemetrexed toxicity. Thus, [the ordinary artisan] would have reasonably expected B_{12} pretreatment to be effective in reducing pemetrexed toxicity.

Id. at 23 (citing Ex. 1077 ¶¶ 47, 51).

Petitioner contends that the prior art in fact suggested that pemetrexed toxicity could be reduced with vitamin B12 supplementation. *Id.* (citing Ex. 1077 ¶¶ 51–52). Petitioner relies on Calvert 1999 for its teaching that a

reduction in either vitamin B12 or folate will result in an increase in plasma levels of homocysteine, and that the measurement of pretreatment levels of homocysteine are a sensitive way to predict toxicity associated with pemetrexed treatment. *Id.* (citing Ex. 1014, 8–9). Petitioner relies also on Zervos for essentially the same proposition. *Id.* at 23–24 (citing Ex. 1016, 256a, Abstract 907).

In addition, Petitioner asserts, the prior art taught that subjects with vitamin B12 levels on the lower side of normal did not achieve full response to folic acid unless vitamin B12 was also given. *Id.* at 24 (citing Ex. 1063, 1277S; Ex. 1077 ¶ 53; Ex. 1019, 1109). Thus, Petitioner asserts, the ordinary artisan "would have been motivated to maximize pretreatment homocysteine reduction by administering folic acid and B_{12} to patients at risk for pemetrexed toxicity." *Id.* (citing Ex. 1077 ¶ 62). Dr. Niyikiza's work, Petitioner contends, "says *nothing one way or the other* regarding whether B_{12} causes elevated homocysteine and pemetrexed toxicity." *Id.* (citing Ex. 1076, 116:12–20; 1077 ¶¶ 51–52). That may be due in part, Petitioner alleges, to the fact that approximately ten percent of patients with B12 deficiency do not present with elevated MMA, the biomarker studied by Dr. Niyikiza. *Id.* (citing Ex. 1017, 97; Ex. 1077 ¶¶ 51, 53).

Thus, Petitioner asserts, "[k]nowing that B_{12} deficiency can cause elevated pretreatment homocysteine and pemetrexed toxicity, this concern would have further motivated [the ordinary artisan] to pretreat pemetrexed patients with both B_{12} and folic acid." *Id.* at 25 (citing Ex. 1076, 41:5–12; Ex. 1077 ¶¶ 62–68). "Moreover, [the ordinary artisan] would supplement with B_{12} to safely increase the effect of folic acid supplementation,

regardless of any correlation between B12 alone and toxicity." *Id.* (citing Ex. 1077 ¶ 51).

Additionally, according to Petitioner, even if the ordinary artisan would not view low vitamin B12 status as causing pemetrexed toxicity, the prior art also "strongly encouraged B_{12} pretreatment for safely administering folic acid." *Id.* (citing Ex. 1077 ¶¶ 62–65). As admitted by Dr. Zeisel, Petitioner argues that the ordinary artisan would have also considered supplementing with vitamin B12 when supplementing with folic acid to avoid masking, which occurs "when folate supplementation appears to alleviate the symptoms of a B_{12} deficiency, thus hiding the B_{12} deficiency and leading to dangerous conditions such as megaloblastic anemia and irreversible neuropathy." *Id.* at 25–26 (citing Ex. 1076, 98:4–17; Ex. 1019, 1104; Ex. 1020, 767–68; Ex. 2067, 321; Ex. 1100, 1479; Ex. 1094, 9; Ex. 1077 ¶ 51).

Petitioner asserts further that the ordinary artisan would have been sensitive to a vitamin B12 deficiency in patients being treated with pemetrexed, a significant portion of which would be elderly and at risk for such a deficiency. *Id.* at 26 (citing Ex. 1078 ¶¶ 58–67; Ex. 1019, 1109; Ex. 1072, 277; Ex. 1094, 9; Ex. 1077 ¶ 51). Additionally, cancer patients are also known to suffer from such deficiencies. *Id.* (citing Ex. 1074, 208; Ex. 1061, 810; Ex. 1078 ¶¶ 66–67, 76–77; Ex. 1077 ¶ 51).

Moreover, Petitioner contends that the ordinary artisan would not have been concerned with a vitamin B12 methyl trap. *Id.* at 27. According to Petitioner, Patent Owner's experts admitted that the issue of the methyl trap is rare, and is not supported by clinical data. *Id.* (citing Ex. 1075, 343:9; Ex. 1076, 145:17–22). Petitioner contends further that the trap would only

be an issue for vitamin B12 deficient patients, and the ordinary artisan would know how to identify those patients by testing. *Id.* (citing PO Resp. 7–8; Ex. 1078, ¶¶ 52, 54, 75). Thus, the ordinary artisan would have had no concerns using vitamin B12 and obtaining the synergistic effects with folic acid in non-B12 deficient patients. *Id.* (citing Ex. 1078 ¶¶ 53–56).

Petitioner contends also that Patent Owner has failed to provide a single reference demonstrating that vitamin B12 would encourage cancer growth in humans, including those receiving pemetrexed, noting that Dr. Zeisel admitted that he is not aware of such a reference. *Id.* at 28 (citing Ex. 1076, 145:17–22). Petitioner argues that "[i]n weighing the risks, [the ordinary artisan] would have determined that the risk of pemetrexed toxicity in a B_{12} deficient patient was much more serious and credible than any risk of B_{12} supplementation, and so would have considered it obvious to administer B_{12} along with folic acid to reduce pemetrexed toxicity." *Id.* at 29 (citing Ex. 1077 ¶¶ 41, 51, 53, 62; Ex. 1078 ¶¶ 85–87).

In response to Petitioner's statement that the ordinary artisan could test for vitamin B12 deficiency, and would then use vitamin B12 in non-vitamin B12 deficient patients, Patent Owner asserts that is a "startling position[ ]," as Petitioner also argues that the reason for using vitamin B12 is that pemetrexed patients may have a deficiency in vitamin B12. Sur-reply 6–7.

After carefully considering Petitioner and Patent Owner's arguments and evidence, as discussed above and for the reasons set forth below, we determine that although the evidence of record supports pretreatment with folic acid before administration of pemetrexed disodium, it does not support

pretreatment with a methylmalonic acid lowering agent, such as vitamin B12.

Initially, we note that Petitioner's rationale for pretreating with a methylmalonic acid (MMA) lowering agent, such a vitamin B12, before administering pemetrexed is "to lower MMA levels, elevated homocysteine levels, and to reduce pemetrexed toxicity." Pet. 28–29 (citing Ex. 1025 ¶ 121). In support, Petitioner cites the Declaration of its expert, Dr. Bleyer, who testifies that "vitamin B12 deficiency results in elevated levels of methylmalonic acid." Ex. 1025 ¶ 121 (citing Ex. 1017, 92–93). The Allen reference supports that testimony, teaching that 95% of vitamin B12 deficient patients had elevated levels of MMA, as well as homocysteine. Ex. 1017, 92–93. According to Allen, even patients with mild vitamin B12 deficiency "had marked elevations (>3 S.D. above the mean for normal subjects) of both serum methylmalonic acid and homocysteine." *Id.* at 93. The testimony is also supported by Refsum, which teaches that serum MMA "is a specific measure of disturbances of [vitamin B12] metabolism." Ex. 1012, 412.

In addition, Dr. Bleyer testifies that the prior art supports that "both methylmalonic acid levels and homocysteine levels be measured to accurately assess the severity of vitamin B12 deficiency." Ex. 1025 ¶ 126. According to Dr. Bleyer:

> From the relevant literature available at the time of the '209 alleged invention, as explained above, [the ordinary artisan] would have understood that administering folic acid alone would result in vitamin B12 deficiency because remethylation of homocysteine requires both folic acid and vitamin B12, and that vitamin B12 deficiency would raise methylmalonic acid levels.

Id. ¶ 127. That is, if a patient is just deficient in folic acid, only homocysteine levels would be raised, but if the patient is deficient in vitamin B12 as well, they would have increased levels of homocysteine *and MMA*. Thus, we find that the preponderance of the evidence of record supports the finding that if a patient is vitamin B12 deficient, that patient would have elevated levels of both homocysteine and MMA.

As noted by Patent Owner, (PO Resp. 10–11), Niyikiza, which looked at both homocysteine and MMA levels, stated that "[s]tepwise regression modelling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA [i.e., pemetrexed]." Ex. 1008, 126–27, Abstract 609P. Although teaching that "[t]oxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels," Niyikiza also teaches that homocysteine and albumin levels "did not appear to change from baseline during treatment with MTA." *Id.* Importantly, although Niyikiza looked at MMA plasma levels, Niyikiza does not teach that MMA levels correlated with toxicity, or that they changed during treatment.

Niyikiza II reports similar results. Niyikiza II teaches that "[b]ecause earlier studies with other antifolates had suggested that nutritional status may play a role in the likelihood that a patient will experience severe toxicity, levels of the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured at baseline and once each cycle thereafter." Ex. 2015, 558a, Abstract 2139. After performing a statistical analysis, Niyikiza II teaches that there was a correlation with toxicity and pretreatment homocysteine levels, although maximum homocysteine levels

did not appear to change from baseline during treatment. *Id.* Niyikiza II teaches further that "[m]aximum cystathionine levels doubled from baseline during treatment with MTA," but that "[n]o correlation between toxicity (CTC Grades as defined above) and the remaining pre-specified predictors [which include the vitamin metabolites] was seen." *Id.* Again, Niyikiza II does not teach that MMA levels correlated with toxicity, or that they changed during treatment.

That finding is supported by the testimony of Patent Owner's expert, Dr. Chabner. Dr. Chabner testifies:

> Niyikiza II also states, "No correlation between toxicity (CTC Grades as defined above) and the remaining pre-specified predictors was seen." Because Niyikiza II discloses that methylmalonic acid ("MMA") was one of the pre-specified predictors, the [ordinary artisan] would understand this disclosure to mean that methylmalonic acid levels were not a predictor of pemetrexed-induced toxicity. Because the [ordinary artisan] would recognize that MMA was the unique marker for a vitamin B12 deficiency (as opposed to homocysteine, which could indicate a folic acid deficiency or a vitamin B12 deficiency), the [ordinary artisan] would understand this disclosure to mean that there was no correlation observed between a vitamin B12 deficiency and pemetrexed-induced toxicity.

Ex. 2120 ¶ 106. Thus, as the Niyikiza Abstracts do not teach an increase in MMA levels during administration of pemetrexed and, in fact, do not even teach that there is a correlation of MMA levels with MTA toxicity, the Niyikiza Abstracts do not supply a reason to lower those levels by pretreatment with an MMA lowering agent before the administration of pemetrexed. That finding is also supported by Zervos, which teaches that eight patients administered pemetrexed that were found to be folate deficient

had elevated levels of homocysteine and cystathione, but were found to have normal levels of methylmalonic acid. Ex. 1016, 256a, Abstract 907.

We note that the Petition did not cite Hammond I as an additional reason to also pretreat with vitamin B12 along with folic acid, and, thus, Petitioner cannot rely on new argument and evidence in its Reply to remedy any deficiency in the obviousness challenge as set forth in the Petition. *See* 37 C.F.R. § 42.23(b); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'"). Moreover, even if we were to consider the argument, we would not find it persuasive. We acknowledge that Hammond I teaches that some patients had methylmalonic acid levels on the high side of normal. Ex. 1022, 129, Abstract 620P. But Hammond I only recommends supplementation with folic acid, and not vitamin B12. *Id.* Thus, Hammond I is not inconsistent with the Niyikiza Abstracts, which did not find that methylmalonic acid levels correlated with pemetrexed toxicity, and we find that Hammond I does not provide a reason to pretreat with vitamin B12 in addition with folic acid before administration of pemetrexed.

Petitioner relies on EP 005 as additionally providing a reason to pretreat with a MMA lowering agent as well as folic acid before administration of pemetrexed. Petitioner points to where EP 005 teaches that "'it is known that vitamin B_6, vitamin B_{12} and folate play a role in regulating the methionine-homocysteine pathway and controlling levels of homocysteine,' such that supplementation with these vitamins is appropriate 'in the treatment of raised homocysteine levels induced nutritionally or . . .

in combination with a B_6 or folate antagonistic drug' or in the case of 'leukemia [or] other cancers.'" Reply 21 (alteration in original) (quoting Ex. 1010, 3, 9). Specifically, Petitioner argues that the prior art taught that "supplementing a patient with both folic acid and [vitamin] B_{12} was significantly more efficacious than supplementing with either vitamin alone," and that was known to be true even in patients with homocysteine levels in what would be considered normal amounts. *Id.* at 20–21 (citing Ex. 1077 ¶¶ 51, 53; Ex. 1063, 1277S–78S; Ex. 1099, 190; Ex. 1019, 1109; Ex. 1010, 18). Dr. Bleyer testifies that the ordinary artisan "would also want to supplement with B12 in order to avoid masking the serious and well-known condition that occurs when folate supplementation appears to alleviate the symptoms of a B12 deficiency, thus hiding the B12 deficiency and allowing it to worsen and result in dangerous conditions such [as] irreversible neuropathy." Ex. 1077 ¶ 51a. Dr. Bleyer testifies also that the ordinary artisan would understand that 5–10% of patients deficient in vitamin B12 cannot be detected using MMA testing. *Id.* ¶ 53.

EP 005 does teach:

> The invention is applicable to the lowering of total homocysteine blood levels if elevated by any known cause, including genetic causes (e.g. enzyme polymorphism) diets, drugs or depressed activity levels of folate, vitamin B6, vitamin B12 or any combination of these due to whatever cause, pregnancy, chronic renal failure, psoriasis, occlusive vascular disease, chronic liver disease, homocysteine-associated psychiatric problems. Drugs which induce elevated homocysteine levels include anticonvulsant drugs, xanthine bronchodilators, (e.g. theophylline), methotrexate, nitrous oxide, and many others.

Ex. 1010, 4:43–48. EP 005 teaches also that "[e]xamples of other situations in which blood homocysteine levels may be elevated are the following: post-

menopausal women, liver failure, leukemia, other cancers, chronic renal failure." *Id.* at 9:54–56.

As noted by Patent Owner (PO Resp. 41), however, EP 005 is concerned with the vascular effects of elevated homocysteine levels, such as myocardial and cerebral infarction. Ex. 1010, 2:4–6. In addition, as also noted by Patent Owner (PO Resp. 41), EP 005 does not exemplify the treatment of any cancer patients, which Petitioner's expert, Dr. Bleyer, does not dispute. Ex. 2027, 207–08. EP 005 also does not discuss antifolates generally, but only lists methotrexate as a drug that may increase homocysteine levels, and mentions leukemia and "other cancers" as causes of elevated homocysteine levels. Thus, we agree with Patent Owner (PO Resp. 42) that EP 005 does not provide any information on how pretreatment with folic acid and vitamin B12 would impact the effects of methotrexate on cancer, or any associated toxicities.

Given the lack of those teachings in EP 005 as to how pretreatment with folic acid and vitamin B12 would impact the effects of methotrexate on cancer, as well as EP 005 defining elevated homocysteine levels as greater that 16.3 µM, and the Niyikiza Abstracts teaching that homocysteine levels of greater than or equal to 10 µM correlate with elevated toxicities, i.e., including homocysteine levels considered normal in EP 005 (i.e., between 10 µM and less than 16.3 µM homocysteine), we find that EP 005 would not provide a reason to pretreat with folate to reduce toxicity, much less with vitamin B12, before the administration of pemetrexed. *See L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1065 (Fed. Cir. 2017) (Board's finding was not supported by substantial evidence, where a particular condition was only mentioned once, and that

there was no data supporting a causation theory); *see also* Reply 29 (noting that Patent Owner's expert, Dr. Zeisel, admitted that the ordinary artisan would not give weight to a reference that does not contain data).

Petitioner further relies on background references, such as Calvert 1999, as showing that low amounts of either vitamin B12 or folate will result in elevated homocysteine. Reply 23–24 (citing Ex. 1014, 8–9; Ex. 1016, 256a, Abstract 907; Ex. 1063, 1277S; Ex. 1019, 1109). Petitioner argues that based on those teachings, the ordinary artisan would have had a reason to administer both folic acid and vitamin B12 to ensure maximum reduction of pretreatment homocysteine levels. *Id.* at 24–25. Petitioner's counsel acknowledged that our reviewing court found Calvert 1999 to "merely note in passing that vitamin B12 can be related to homocysteine levels and folate biochemical pathways." Tr. 147:13–19[27] (quoting *Eli Lilly*, 845 F.3d at 1375). Our reviewing court further found no testimony to support the contention that background references including Calvert 1999 "would motivate a skilled artisan to arrive at the claimed use of vitamin B12 as a pretreatment for pemetrexed, especially in view of the evidence of gaps and concerns regarding the prior art discussed above." *Eli Lilly*, 845 F.3d at 1375; Tr. 147:19–22. Petitioner contends that it now has that testimony. Tr. 147:22–148:1. We, however, disagree that the testimony offered by Petitioner is sufficient to overcome the gaps in the prior art, including the "missing link between vitamin B12 deficiency and pemetrexed toxicity" and nothing that "describe[s] cancer patients being provided with vitamin B12

[27] We acknowledge that the district court standard (clear and convincing evidence) for finding a claim invalid is different than ours (preponderance of the evidence), and we have reviewed the evidence of record using our standard.

supplementation prior to receiving any antifolate, with or without folic acid." *Eli Lilly*, 845 F.3d at 1373–74 (internal quotation marks omitted).

As to Dr. Bleyer's testimony, we do not find it to be persuasive on this issue. In particular, we note that Dr. Bleyer testified:

> [The ordinary artisan] in 1999 would have been particularly sensitive to B12 deficiencies causing elevated homocysteine and pemetrexed toxicity since patients being treated with pemetrexed were more likely to suffer from B12 deficiencies, especially with repeated pemetrexed administrations (recall that 30% of patients in the Phase II trial reported by Rusthoven had to stop therapy due to toxicity. (Ex. 1011 at 1194, 1198.) There are several reasons for this likelihood:
>
> i. The cancers for which pemetrexed is a treatment (e.g., lung and pancreatic cancer) are more likely to occur in older adults, and the elderly have a higher incidence of B12 deficiencies than the general population. (Ex. 1072 at 277; Ex. 1075 at 348:4-8; Ex. 1076 at 149:25-150:3.)
>
> ii. Patients with cancer are also more likely to suffer from B12 deficiencies, as are patients undergoing chemotherapy (such as cisplatin, which is often given in conjunction with pemetrexed) that causes nausea and malnutrition. (Ex. 1074 at 208; Ex. 1061 at 810.)
>
> iii. Dr. Chabner's concern regarding the methyl trap assumes that a portion of the patients receiving pemetrexed would be B12 deficient since the methyl trap is only a concern in B12 deficient patients. (Ex. 2120 ¶ 123; Ex. 1076 at 105:7-108:4.)

Ex. 1077 ¶ 51c.

As discussed earlier, Patent Owner provides evidence that a deficiency in vitamin B12 in a patient causes a "methyl trap," such that administering even a small amount of vitamin B12 could lead to the release of a large amount of folate, thereby potentially causing a reduction in the

anti-cancer properties of the antifolate drug. PO Resp. 7–8, 20–22, 51. With that in mind, Dr. Bleyer's testimony appears to be internally inconsistent. That is, in (i) and (ii) of the testimony above, Dr. Bleyer testifies that the cancer patients being treated are more likely to have vitamin B12 deficiencies, but then in (iii) testifies that the methyl trap is only a concern in relation to vitamin B12 deficient patients. Ex. 1077 ¶ 51c. That interpretation is supported by Petitioner's Reply, which argues that the methyl trap is only a concern for vitamin B12 deficient patients, and "[s]ince [the ordinary artisan] would have known how to identify B_{12}-deficient patients by testing (Paper 33-8), [the ordinary artisan] would not refrain from using B_{12}—and thus reaping synergistic benefits with folic acid—in non-B_{12}-deficient patients. (Ex. 1078 ¶¶53-56)." Reply 27.

Thus, it is unclear if Petitioner's rationale is to add vitamin B12 to folate when pretreating before administration of pemetrexed because cancer patients are more likely to be deficient vitamin B12, and B12 deficiency may be masked, or if Petitioner's rationale is that one would only add vitamin B12 to folate in pretreating before administration of pemetrexed to those patients that are known not to be deficient in vitamin B12. In other words, Petitioner and its witness seem to suggest that an ordinary artisan would have been motivated to administer vitamin B12 to address vitamin B12 deficiencies that could result from treatment with pemetrexed disodium, but at the same time also would know not to give vitamin B12 to patients who are vitamin B12-deficient due to the "methyl trap" issue.

As for treating patients not known to be deficient in vitamin B12, Petitioner does provide sufficient evidence[28] supporting its assertion of the "synergistic benefits [of using vitamin B12] with folic acid—in non-B12-deficient patients." Reply 27. Although Petitioner cites to Brönstrup[29] and EP 005 as teaching synergistic benefits (*id.* at 21 (citing Ex. 1019, 1109; Ex. 1010, 18)), as Petitioner's counsel clarifies, those references only refer to high homocysteine levels generally—they do not further specify whether the high homocysteine levels are due to low folic acid, low vitamin B12, or both (Tr. 163:12–164:22). Accordingly, Petitioner does not provide sufficient evidence and explanation to support a conclusion as to why the ordinary artisan would have expected to achieve the synergistic benefits taught in Brönstrup and EP 005 in the specific instance where a patient does not have low levels of vitamin B12.

> As for the masking concern, Dr. Bleyer testifies also that
>
> when supplementing a pemetrexed patient with folic acid—already documented in the prior art at reducing pemetrexed toxicity—[the ordinary artisan] would also want to supplement with B12 in order to avoid masking the serious and well-known condition that occurs when folate supplementation appears to alleviate the symptoms of a B12 deficiency, thus hiding the B12 deficiency and allowing it to worsen and result in dangerous conditions such irreversible neuropathy. (Ex. 1054 at 1720; Ex. 1076 at 98:4-17.)

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[28] We acknowledge that Petitioner does cite to paragraphs 53 to 56 of Dr. Mason's Reply Declaration (Ex. 1078). Those paragraphs, however, do not address any synergistic effects that may be obtained by administering vitamin B12 along with folic acid in non-vitamin B12 deficient patients.

[29] Anja Brönstrup et al., *Effects of Folic Acid and Combinations of Folic Acid and Vitamin B-12 on Plasma Homocysteine Concentrations in Healthy, Young Women*, 68 AM. J. CLINICAL NUTRITION 1104 (1998) ("Brönstrup") (Ex. 1019).

Ex. 1077 ¶ 51a. However, during deposition, Dr. Bleyer testified that although the prior art, such as the Hammond Abstracts, taught pretreatment with folic acid, he was not aware of any references that taught pretreatment with both folic acid and vitamin B12 before administration of an antifolate. Ex. 2027, 182:20–183:2. The only reference that Dr. Bleyer was aware of that administered both folic acid and vitamin B12, Carrasco, as acknowledged by Dr. Bleyer, administered the combination after treatment with the antifolate methotrexate. *Id.* at 174:16–175:10. Petitioner has not explained that, if it was so well known that treatment with folic acid may mask a vitamin B12 deficiency that could lead to irreversible neuropathy, why the references, such as the Hammond Abstracts, that did teach pretreatment with folic acid to address pemetrexed toxicity did not also pretreat with vitamin B12.

As to Carrasco, Patent Owner argues that reference is not prior art. PO Resp. 44 n.4. Carrasco, Patent Owner further argues, although given vitamin B12 and folic acid while receiving methotrexate chemotherapy, was not pretreated with vitamin B12 and folic acid, but was given vitamin B12 and folic acid after receiving methotrexate to treat megaloblastic anemia, a symptomatic vitamin deficiency. *Id.* at 44 (citing Ex. 1020). Carrasco makes clear, Patent Owner asserts, that vitamin B12 and folic acid were not given to ameliorate the toxicity of the antifolate, but to correct some of the anemia. *Id.* (citing Ex. 1020; Ex. 2120 ¶ 182).

We conclude that we need not determine whether Carrasco is prior art, because even if we assume *arguendo* that it is prior art, we conclude that it is not sufficient to demonstrate that it would have been obvious to pretreat with vitamin B12, as well as folic acid, before administration with pemetrexed.

Carrasco provides data for only one patient, a 45-year old male diagnosed with Philadelphia-positive chronic myelogenous leukemia. Ex. 1020, 767. The patient was treated with methotrexate, and methotrexate "rescue with folinic acid was performed following standard guidelines." *Id.* After treatment with the methotrexate, the patient was found to have acute megaloblastosis, and was treated with folinic acid, folic acid, and vitamin B12. *Id.* at 767–68. Thus, the folic acid and vitamin B12 were administered to treat the acute megaloblastosis. We find, therefore, that Carrasco does not provide sufficient reason to pretreat with folic acid and vitamin B12 before administration with pemetrexed.

We find, therefore, for the reasons discussed above, that Petitioner has not established by a preponderance of the evidence that the ordinary artisan would have pretreated with vitamin B12 as well as with folate before administering pemetrexed to a cancer patient.

Petitioner, in its Reply, contends that Dr. Chabner's testimony that there were a limited number of ways to address pemetrexed toxicity is evidence that the ordinary artisan "would have found it obvious—or at least obvious to try—the folic acid/B_{12} combination to address those patients' toxicity." Reply 4 (citing Ex. 1075, 149:18–152:4, 308:20–310:1). In addition Petitioner asserts that, in discussing the limited alternatives, Dr. Chabner used an improper standard for a reasonable expectation of success of those alternatives, that is, whether an ordinary artisan would have been encouraged to undertake investigation, but then used a higher standard, proof of clinical data, when evaluating a reasonable expectation of success of pretreatment with vitamin B12 and folic acid. According to Petitioner,

this entitles the opinions of Dr. Chabner to little weight. *Id.* at 4–5 (citing Ex. 1075, 136:2–13).

We do not find Petitioner's arguments in this regard persuasive. As noted above, we are able to assess Dr. Chabner's testimony and afford it the appropriate weight when Dr. Chabner's testimony is considered in the context of the evidence of record. In addition, Petitioner's counsel acknowledged that its "obvious to try" argument was not made in the Petition, and other than the one statement reproduced above, is also not fleshed out in the Reply. Tr. 168:13–14 (Counsel for Petitioner admitting that "obvious to try was not in the petition"); *see also id.* at 169:14–170:1 (Counsel for Petitioner stating, in response to a question as to whether the number of identified solutions are predictable, "I don't think the obvious-to-try point is one to get hung up on. Our point is it's obvious"). Moreover, just invoking "obvious to try" does not provide a reason to pretreat with vitamin B12 as well as folic acid before administration of pemetrexed.

Petitioner argues further that three documents also undermine Dr. Chabner's credibility and support the obviousness of the challenged claims. Reply 6. Specifically, Petitioner cites a 1999 letter from Lilly to the FDA,[30] a 2000 letter from Lilly to the FDA,[31] and Hanauske.[32] *Id.*

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[30] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Food & Drug Admin. (Dec. 3, 1999) (Ex. 2103).

[31] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Project Manager, Food & Drug Admin. (Feb. 16, 2000) (Ex. 2107). The page numbers refer to the page numbers added by Patent Owner.

[32] Axel-R. Hanauske et al., *Pemetrexed Disodium: A Novel Antifolate Clinically Active Against Multiple Solid Tumors*, 6 THE ONCOLOGIST 363 (2001) (Ex. 1047) ("Hanauske").

Although Petitioner acknowledges that Lilly's letters to the FDA are not "technically prior art," Petitioner asserts that they are evidence of the knowledge of the ordinary artisan at the time of invention. *Id.* (citing *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580–81 (Fed. Cir. 1983); *In re Wilson*, 311 F.2d 266, 268–69 (CCPA 1962)). Petitioner acknowledges further that although Hanauske "was submitted six months after the effective filing date, it is relevant to obviousness." *Id.* at 6–7 (citing *In re Hogan*, 559 F.2d 595, 605 & n.17 (CCPA 1977); *Ex Parte Raychem Corp.*, 25 USPQ2d 1265, 1268 & n.4 (BPAI 1992) (nonprecedential); *Ex Parte Erlich*, 22 USPQ2d 1463, 1465–66 (BPAI 1992) (nonprecedential)).[33]

> As to Lilly's 1999 letter to the FDA, Petitioner asserts:
>
> > Lilly submitted a brief to the FDA, where patient health turns on the importance of candor and scientific rigor, explaining the rationale for administering folic acid and B_{12} before pemetrexed treatment. In doing so, Lilly cited the teachings of several prior art references at issue here, including Niyikiza (Ex. 1008), Calvert (Ex. 1013, Laohavinij (Ex. 2031), Worzalla (Ex. 1005), Bronstrup 1999 (Ex. 1099), and Hammond (Ex. 1022). (Ex. 2103-19-20; Ex. 1077 ¶¶69-71.)

Id. at 8. And as to Lilly's 2000 letter, Petitioner asserts:

> > Lilly explained to the FDA that the teachings of the prior art justified pretreating with folic acid and B_{12} before and during pemetrexed treatment. This prior art included Worzalla (Ex. 1005), Laohavinij (Ex. 2031), Bronstrup 1999 (Ex. 1099), Morgan 1990 (Ex. 1023). (Ex. 2107, *passim*; Ex. 1077 ¶¶69-71.)

[33] According to Petitioner, it is not arguing that the inventor's path to the invention or how it was achieved are evidence of obviousness; rather, it is citing the FDA letters and Hanauske to show how the ordinary artisan interpreted prior art references around the priority date and to discredit the testimony of Dr. Chabner. Reply 8 n.4.

Id. at 8–9.

According to Petitioner, those documents admit that Hammond teaches the ordinary artisan "that the addition of folic acid supplementation permits pemetrexed dose escalation and ameliorates toxicity." *Id.* at 9. In the face of those letters to the FDA and Hanauske, Petitioner argues that Dr. Chabner rejects Lilly's interpretation of the references it made to the FDA. *Id.* at 9–11.

Again, we do not find Petitioner's arguments in this regard persuasive. As noted above, we are able to assess Dr. Chabner's testimony and afford it the appropriate weight when Dr. Chabner's testimony is considered in the context of the evidence of record. Moreover, we also decline to read the references in view of Lilly's letters to the FDA, which both parties agree are not prior art.

In *KSR*, the Supreme Court reaffirmed that, despite the importance of a flexible and common-sense approach when evaluating obviousness, fact finders "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 550 U.S. at 421. Accordingly, the Federal Circuit has noted, even after *KSR*, fact finders must "still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how *or why* the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (emphasis added).

The prior art referenced by Lilly in its letters to the FDA, as well as what Lilly states about those references, are viewed through the lens of the invention of the Lilly scientists and researchers, i.e., inventors of the '209

patent challenged here. As the case law makes clear, we must look at the prior art and determine what it teaches or suggests to the ordinary artisan without the benefit of the invention, and, importantly, whether the prior art provides a reason to combine the references to arrive at the claimed invention. As discussed above, we find that the prior art does not provide a reason to pretreat with vitamin B12, along with pretreating with folic acid, before the administering pemetrexed to treat cancer.

f. Secondary Considerations

Additionally, factual inquiries for an obviousness determination include secondary considerations based on objective evidence of nonobviousness. *See Graham*, 383 U.S. at 17–18. The totality of the evidence submitted may show that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Before we make our final obviousness determination, we consider the evidence of obviousness anew in light of any evidence of secondary considerations of nonobviousness presented by Patent Owner. *See Graham*, 383 U.S. at 17–18 ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, skepticism, licensing, and praise. *See Graham*, 383 U.S. at 17; *Transocean*, 699 F.3d at 1349.

Patent Owner argues that secondary considerations, and in particular, skepticism of the invention, as well as praise of others, support the patentability of the challenged claims. PO Resp. 54–56 (citing *Leo Pharm. Prods.*, 726 F.3d at 1358).

As to skepticism, Patent Owner argues that Dr. Niyikiza testified in the prior litigation that his idea was met with skepticism, "and was not adopted until after the priority date, when deaths occurred in the Phase III clinical trials." *Id.* at 55 (citing Ex. 2116, 750–58, 760–65, 771–75). Dr. Chabner, before he was retained by Patent Owner, when he was interviewed by the *Wall Street Journal* opined that he thought the vitamin pretreatment regimen for pemetrexed was "crazy." *Id.* at 55–56 (citing Ex. 2091, 3; Ex. 2120 ¶¶ 33h, 225–227).

Patent Owner argues further that "the FDA expressed skepticism about proposals to pretreat pemetrexed patients with vitamins, even after receiving information on safety and efficacy from [Patent Owner]," stating that vitamin pretreatment was at Patent Owner's risk. *Id.* at 56 (citing Ex. 2100, 8044, 8046; Ex. 2103; Ex. 2105; Ex. 2109, 10; Ex. 2108, 2; Ex. 2116, 845). According to Patent Owner, at that time, "in an ongoing phase III pemetrexed trial, an alarming 7% of patients died, apparently due to severe pemetrexed toxicities," threatening to halt further development of the drug. *Id.* at 11 (citing Ex. 2103, 2; Ex. 2107, 16). Thus, Lilly decided to administer low levels of vitamin B12 and folic acid prior to the administration of pemetrexed to try and alleviate those toxicities, even though the FDA was still skeptical. *Id.* at 12 (citing Ex. 2107, 17; Ex. 2116, 798–99, 821–22; Ex. 2104, 1; Ex. 2106; Ex. 2108, 2, 5). Specifically, Patent Owner contends that "the FDA wrote Lilly that '[t]he Medical Officer does

not support adding vitamins to your ongoing pivotal, randomized trial in mesothelioma.'" *Id.* (quoting Ex. 2104, 1) (citing Ex. 2106). Moreover, Patent Owner asserts, even after a meeting between representatives from Lilly, including Dr. Niyikiza, the FDA continued to be skeptical, "asking Lilly '[w]hat is the evidence that folate/ B_{12} repletion will not stimulate tumor growth prior to the administration of chemotherapy?'" *Id*. (alteration in original) (quoting Ex. 2108, 5) (citing Ex. 2108, 2).

As to praise by others, Patent Owner argues that the invention was praised by others after its implementation. *Id.* at 56. Thus, when the pemetrexed Phase III clinical trial was presented at the plenary session of the annual meeting of the American Society of Clinical Oncology, the trial's principal investigator praised Dr. Niyikiza as saving the drug, stating that without Dr. Niyikiza's contribution, "the drug would probably be dead." *Id.* (quoting Ex. 2116, 845).

Petitioner responds that the alleged secondary considerations do not weigh against a conclusion of obviousness. Reply 31–34. Petitioner contends further that Patent Owner misinterprets the statements of the FDA made during the pemetrexed approval process. *Id.* at 32–33. According to Petitioner, "the FDA's characterization of Lilly's late changes to its Phase III clinical trial had nothing to do with the FDA's views on the feasibility of a vitamin pretreatment regimen," rather, "the change was 'at Lilly's risk' because it could leave Lilly without statistically meaningful results even if the trial were successful." *Id.* at 32 (citing Ex. 2109, 10). Thus, the FDA suggested that Patent Owner start a new trial with pemetrexed and vitamins. *Id.*

As to Patent Owner's argument that its principal investigator told Dr. Niyikiza that "the drug would probably be dead without him," Petitioner argues that statement is not corroborated, and Patent Owner "refused to submit Dr. Niyikiza for cross-examination," and the statement is, thus, entitled to little or no weight. *Id.* at 31–32.

Petitioner argues as to Dr. Chabner's statements to the *Wall Street Journal* that those statements are not persuasive evidence of skepticism as Dr. Chabner admitted he would be skeptical until he saw clinical data showing that pretreatment supplementation with folic acid and vitamin B12 worked. *Id.* at 33 (citing Ex. 1075, 198:6–201:11, 204:2–206:2, 209:7–210:2).

We find that the evidence of secondary considerations supports a conclusion that Petitioner has not established by the preponderance of the evidence of record that the challenged claims would have been obvious.

As to Dr. Chabner's statements reported by the *Wall Street Journal*, we acknowledge that it does not support the nonobviousness of the claims, as it pertains only to pretreatment with folic acid, and not pretreatment with both vitamin B12 and folic acid before the administration of the antifolate. Ex. 2091, 3 ("Give all patients folic acid pills in addition to their dose of [pemetrexed]," which Dr. Chabner thought was "crazy"). As discussed above, we find a preponderance of the evidence of record supports a finding that it would have been obvious to pretreat with folic acid, but not vitamin B12. Therefore, Dr. Chabner's statement does not have the required nexus to the claimed invention. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (noting that the proponent of secondary considerations evidence "must establish a nexus between the evidence and the merits of the claimed

invention"); *see also Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) ("In evaluating whether the requisite nexus exists, the identified objective indicia must be directed to what was not known in the prior art . . . . ").

We do, however, find that the skepticism of others, and particularly, the FDA, supports the nonobviousness of the claimed invention. Lilly reported to the FDA in its letter of February 16, 2000, that there were 3 treatment related deaths out of 42, i.e., 7% of the patients died. Ex. 2017, 16. Lilly stated after exploring intervention options and seeking guidance from external experts, the consensus was "that a 7% rate of death in a registration trial is unacceptable and that an intervention should be taken immediately." *Id.* Lilly stated that it felt that investigators would be reluctant to enroll patients in trials without vitamin supplementation, stating that "external consultants have said Ethical Review Boards would be reluctant to approve a trial such as this." *Id.* at 18.

In its December 3, 1999 letter to the FDA, Lilly stated that "[d]rug-related death is highly correlated with severe toxicity." Ex. 2103, 2; *see also id*. at 3 (same). Because of that correlation, and in the interest of patient safety, Lilly recommended supplementation with folic acid and vitamin B12. *Id*. at 3. In response to Lilly's letter of December 22, 1999, the FDA responded that the "medical officer does not support adding vitamins to the ongoing mesothelioma registration trial[,] . . . and does not support the proposed plan to add vitamins to this pivotal trial." Ex. 2106. The FDA provided further reasons in a letter dated December 21, 1998, which included concerns not just about the statistical plan, but also that the information that had been provided "about the toxicities in the trial . . . does

not appear to support the addition of vitamins." Ex. 2104, 1. The FDA stated that "[i]f you believe that vitamin administration will be an important aspect of the MTA label, this may be an important trial that can provide convincing evidence with regard to efficacy and safety of MTA with and without vitamins." *Id.* at 1–2. In addition, the FDA had stated earlier in a meeting held between Lilly and the FDA on September 25, 1998, that "the addition of the vitamins to the MTA arm without data that efficacy is not reduced is risky." Ex. 2100, 8044. In the meeting minutes of March 1, 2000, between the FDA and Lilly, the FDA stated that although it shared Lilly's concerns regarding toxicity, the addition of vitamins was at Lilly's risk. Ex. 2108, 2. Thus, one of the options proposed by the FDA was to close the trial and conduct a new Phase I trial with pemetrexed and vitamins. *Id.* That is, one of the FDA's concerns in that regard was having a well-controlled trial. *Id.* at 3.

We find that a preponderance of the evidence of record supports a finding that there was skepticism by others, and in particular, the FDA. In that regard, we note that pemetrexed was already in trial when a 7% death rate was seen. Thus, a reasonable inference is that neither Lilly, nor apparently the FDA, initially thought that vitamin supplementation with folic acid or vitamin B12 before administration of the pemetrexed for treatment would be necessary to ameliorate the toxicity of the antifolate. *See, e.g.*, Tr. 38:4–8) (Counsel for Patent Owner stating that "Lilly went into its phase three registration trial without using any vitamin supplementation and only changed its approach after the priority date when it saw an unacceptable number of deaths in the study that it had not anticipated"). It was not until the death rate rose to 7%, raising ethical concerns, that Lilly

considered such pretreatment. Lilly was willing to jeopardize its ongoing clinical trial in face of the FDA's statement that any change would be at Lilly's risk and, yet, Lilly added pretreatment with folic acid and vitamin B12 to ameliorate the toxicity seen in its trial. Even then, the FDA stated that the information provided did not appear to support the addition of vitamins. Thus, even in view of the death rate seen by Lilly in the clinical trials, the FDA was not convinced vitamin supplementation was warranted.

That is, we do not disagree with Petitioner that the part of the FDA's concern about Lilly changing its Phase III clinical trial was obtaining statistically relevant evidence. Reply 32 (citing Ex. 2109, 10). At the same time, however, the FDA also indicated that information provided about the toxicities did not appear to support the addition of vitamins. Ex. 2104, 1.

Finally, we also find that Dr. Niyikiza's testimony at the district court as to the praise of others does not add anything to the skepticism of the FDA, as all Dr. Niyikiza states is that the principal investigator stated that "[i]f you didn't do it, this drug would probably be dead." Ex. 2116, 845:16–25. As that statement was made by the principal investigator, it is not a statement by an "other," but someone who was part of the same research team. *See In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016) ("While 'praise in the industry for a patented invention, and specifically praise from a competitor tends to "indicate that the invention was not obvious,"' self-serving statements from researchers about their own work do not have the same reliability." (quoting *Power-One v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1352 (Fed. Cir. 2010))).

iii. Conclusion as to Obviousness

We determine, therefore, that although Petitioner has demonstrated that the preponderance of the evidence of record supports that it would have been obvious to the ordinary artisan at the time of invention to pretreat with folic acid before administering pemetrexed sodium to treat cancer, Petitioner has failed to demonstrate by a preponderance of the evidence of record that it also would have been obvious to the ordinary artisan to pretreat with vitamin B12 as well. In addition, we agree with Patent Owner that the preponderance of the evidence of record supports a finding that the secondary indicia of skepticism of others, and, in particular, the FDA, supports a conclusion of nonobvious. Thus, weighing all of the evidence of obviousness of record, we conclude that Petitioner has failed to demonstrate that challenged independent claims 1 and 12 of the '209 patent were rendered obvious by the combination of Niyikiza, the '974 patent, and EP 005. As claims 1 and 12 are the only independent claims, and, thus, all the claims require pretreatment with vitamin B12, we determine that Petitioner has not demonstrated the unpatentability of any of the challenged claims over the combination of Niyikiza, the '974 patent, and EP 005 by a preponderance of the evidence of record.

D. Petitioner's Motion to Exclude

Petitioner seeks to exclude Patent Owner's Exhibits 2120 and 2116. Mot. Exclude 1.

Exhibit 2120 is the declaration testimony of Dr. Bruce Chabner. *Id.* Petitioner argues that Dr. Chabner used incorrect legal standards, is unsubstantiated, and is based on subjective beliefs. *Id.* at 1–7. Petitioner's objection, however, goes more to the weight of the testimony, rather than its

admissibility. We, therefore, *deny* Petitioner's Motion to Exclude as to Exhibit 2120.

Exhibit 2116 is the trial testimony of Dr. Niyikiza, as provided in district court. Petitioner argues that the testimony should be excluded as hearsay, improper expert testimony, and an improper attempt to circumvent the cross-examination.[34] *Id.* at 7–12.

As noted by Patent Owner, however, Petitioner put the district court's findings of fact into evidence. Opp. Mot. Exclude 9 (citing Ex. 1028). Patent Owner notes further that it filed the trial testimony in its entirety. *Id.* at 15 (citing Ex. 2125).

We determine that Dr. Niyikiza's testimony relates to the district court's findings of facts filed by Petitioner, and, thus, we also *deny* Petitioner's Motion to Exclude as to Exhibit 2116.

III. CONCLUSION

After considering Petitioner's and Patent Owner's positions and evidence, we conclude that Petitioner has not demonstrated by a

[34] Petitioner notes that with the Board's authorization, it filed a motion seeking to depose Dr. Niyikiza, but that we have not ruled on that motion and Dr. Niyikiza has not been provided for deposition. Mot. Exclude 10–11. Given that we are at the final written decision, we *deny* Petitioner's motion as moot. We note that we placed no reliance on Exhibit 2116 in this Decision, and, therefore, determine that there has been no prejudice to Petitioner.

preponderance of the evidence that claims 1–22 of the ’209 patent are unpatentable.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has failed to show by a preponderance of the evidence that claims 1–22 of the ’209 patent are unpatentable under 35 U.S.C. § 103(a);

FURTHER ORDERED that Petitioner’s Motion to Exclude is *denied*; and

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

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