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Paper No. 11
Entered: October 5, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC., APOTEX INC., APOTEX CORP., EMCURE PHARMACEUTICALS LTD., HERITAGE PHARMA LABS INC., HERITAGE PHARMACEUTICALS INC., GLENMARK PHARMACEUTICALS, INC., USA, GLENMARK HOLDING SA, GLENMARK PHARMACEUTICALS, LTD., MYLAN LABORATORIES LIMITED, TEVA PHARMACEUTICALS, USA, INC., FRESENIUS KABI USA, LLC, and WOCKHARDT BIO AG,
Petitioner,

v.

ELI LILLY & COMPANY,
Patent Owner.

Case IPR2016-00318[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

[1] Cases IPR2016-01340, IPR2016-01393, and IPR2016-01429 have been joined with the instant proceeding.

I. INTRODUCTION

Sandoz Inc. 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 2 ("Pet."). Eli Lilly & Company ("Patent Owner" or "Lilly") filed a Preliminary Response to the Petition. Paper 11 ("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, we instituted trial on June 16, 2016, as to all of the challenged claims of the '209 patent. Paper 14 ("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., Apotex Corp., Emcure Pharmaceuticals Ltd., Heritage Pharma Labs Inc., Heritage Pharmaceuticals Inc., Glenmark Pharmaceuticals Inc., USA, Glenmark Holding SA, Glenmark Pharmaceuticals Ltd., and Mylan Laboratories Limited requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01429, and joinder to the instant proceeding. IPR2016-01429, Papers 2 and 3. On October 6, 2016, the Board instituted *inter partes* review in that case, and granted joinder. IPR2016-01429, Paper 11. Teva Pharmaceuticals USA, Inc. and Fresenius Kabi USA, LLC requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01340, as well as joinder to the instant proceeding. IPR2016-01340, Papers 2 and 3. *Inter partes* review was instituted in that case and joinder granted on October 6, 2016. IPR2016-

01340, Paper 9. Finally, Wockhardt Bio AG also requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01393, and joinder to the instant proceeding. IPR2016-01393, Papers 1 and 3. *Inter partes* review was instituted and joinder granted on November 21, 2016. IPR2016-01393, Paper 9. We collectively refer to all enjoined Petitioners in this Final Written Decision as "Petitioner."

Patent Owner filed a Response (Paper 36, "PO Resp."), Petitioner filed a Reply (Paper 49), and Patent Owner filed a Sur-reply (Paper 68). In addition, Petitioner filed a Motion to Exclude (Paper 64, "Mot. Exclude"), to which Patent Owner filed an Opposition (Paper 72, "Opp. Mot. Exclude"), and Petitioner filed a Reply (Paper 77). Oral hearing was held on March 16, 2017, and a transcript of that hearing has been entered into the record. Paper 81 ("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. Sandoz Inc.*, No. 1:14-cv-2008 (S.D. Ind.) (filed Dec. 5, 2014). Pet. 2–3; Paper 5, 2–3.

The ’209 patent also has been challenged in IPR2016-00237 and in IPR2016-00240 by Neptune Generics, LLC. IPR2016-01190, IPR2016-01335, and IPR2016-01341 have been joined with IPR2016-00237, and proceedings IPR2016-01191, IPR2016-01337, and IPR2016-01343 have been joined with IPR2016-00240.

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. 1047, 35.[2] 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. 1004 ¶¶ 28–29, 31.

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

[2] 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.

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").[3] Ex. 1015, 129, Abstract 620P.

C. Illustrative Claims

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

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

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 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 coadministering 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

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[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. 1013) ("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. 1015) ("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. 1005) ("the '974 patent").

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 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. Niyikiza and Niyikiza II 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.

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[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. 1006) ("Niyikiza" or "Niyikiza I").

[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. 1016) ("Niyikiza II").

The court further explained that in Niyikiza and Niyikiza II, there was no correlation between toxicity and other measured variables, including MMA, which suggested at the time that there was no correlation between toxicity 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 folate 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 B12 deficiency was not the problem in pemetrexed toxicity" and "would not have used vitamin B12 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 indicated a vitamin B12 deficiency—instead, MMA levels specifically indicate 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 B12 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. 1064,[11] 138:7–8).

The Federal Circuit found that two prior art references, one of them being Calvert 1999,[12] which Petitioner relies on in its challenges 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 Challenges

We instituted trial based on the following grounds of unpatentability (Dec. Inst. 21):

References	**Basis**	**Claims Challenged**
Calvert, Niyikiza I, Worzalla, EP 005, [13] and the '974 patent	§ 103(a)	1–22

[11] Petitioner did not file Exhibit 1064 in this proceeding. Paper 75, 9. The same exhibit is filed as Exhibit 1051 in IPR2016-00237.

[12] 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. 1007) ("Calvert 1999" or "Calvert").

[13] Willem Jacob Serfontein, EP 0 595 005 A1, published May 4, 1994 (Ex. 1033) ("EP 005").

References	Basis	Claims Challenged
Calvert, Niyikiza I, Hammond I, EP 005, and the '974 patent	§ 103(a)	1–22

Petitioner relies also on the Declaration of Ron D. Schiff, M.D., Ph.D. (Ex. 1004), as well as the Reply Declarations of Dr. Schiff (Ex. 1075), David B. Ross, M.D, Ph.D., M.B.I. (Ex. 1093) and Patrick J. Stover, Ph.D. (Ex. 1091).

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. 9–10 (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)). For purposes of this Decision, we determine that the only claim term that is in controversy is the term "patient."

Petitioner argues that the claim term "patient" should be construed as encompassing mammals. Pet. 18–21. Specifically, Petitioner notes that the Specification of the '209 patent does not define the term "patient," and uses the terms "mammal" and "patient" interchangeably. *Id.* at 19 (citing (Ex. 1001, 4:4–27; 6:35–54). Petitioner asserts further that the prosecution history supports construing "patient as mammal," asserting that Patent Owner "knew how to limit the scope of the claims to treatment of a 'human' when that was the intention." *Id.* at 19–20 (citing Ex. 1024, 38; Ex. 1002, 3).

Patent Owner responds that the claim term "patient" should be construed in accordance with "its ordinary and customary meaning" as would be understood by the ordinary artisan of "a human undergoing medical treatment." PO Resp. 14–15 (citing Ex. 2120 ¶¶ 28–29). Patent

Owner asserts that construction has been adopted by Petitioner's expert, and is supported by the Specification of the '209 patent. *Id.* at 15–16 (citing Ex. 2026, 345–347, 349; Ex. 1001, 6:57–67, 7:1, 7:41–42, 7:46–47, 7:66, 8:15, 8:39, 8:42–45, 8:49, 8:55–58, 9:14–17, 9:21–55, 9:21–55, 10:17–28 (noting that laboratory mice in the test examples are referred to as "animals," whereas, when discussing clinical studies, the Specification refers to "patients")).

We conclude[14] that the ordinary artisan, in view of the Specification of the '209 patent, would understand that when referring to a "patient" in the claims, that patient include mammals, and is not limited to human patients. In that regard, we agree with Petitioner that the Specification uses "mammal" and "patient" interchangeably. *See* Ex. 1001, 4:4–27; 6:35–54. We acknowledge that the Specification refers to the test mice as animals, *see id.* at 6:57–7:1, and refers to humans as patients when discussing clinical trials, *see id.* at 10:43–52. We, however, may not limit the claims to a particular embodiment, but instead we must apply the broadest reasonable interpretation consistent with the Specification's interchangeable use of the terms "mammal" and "patient."

B. Level of Ordinary Skill in the Art

Petitioner contends:

> [T]he person of ordinary skill in the art ("POSA") at the time of the alleged invention would have been a medical doctor experienced in oncology with knowledge and/or several years of experience regarding the use of antifolates in the treatment of

[14] We note that the analysis of the patentability of the claims, below, would be the same under either Petitioner's or Patent Owner's proposed construction.

> cancer and additional qualifications or experience in the field of nutritional sciences involving vitamin deficiencies.

Pet. 18 (citing Ex. 1004 ¶ 13).

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. The [ordinary artisan] 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. 13–14.

Patent Owner notes that the definition of the ordinary artisan as provided by Petitioner's expert, Dr. Schiff, "is generally consistent with Dr. Chabner's definition." PO Resp. 14. Thus, we determine we need not distinguish between the two definitions provided. We note further 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, to the extent there may be minor differences, our analysis would be the same under either Petitioner's or Patent Owner's definition of the ordinary artisan.

C. Obviousness over Calvert, Niyikiza I, and Worzalla or Hammond I, in addition to EP 005, and the '974 patent[15]

Petitioner contends that claims 1–22 are rendered obvious by the combination of over Calvert, Niyikiza I, Worzalla or Hammond I, EP 005, and the '974 patent. Pet. 27–59. 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. 17–57.

i. Overview of the Prior Art Relied Upon

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

a. Calvert (Ex. 1007)

Calvert provides an overview of folate metabolism and describes features relevant to the action and toxicities of antifolate cancer agents. Ex. 1007, 3. According to Calvert, the development of cancer therapeutics has been linked intimately to the study of folic acid metabolism and the action of antifolate drugs. *Id.* Calvert 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 also discusses, however, how it had been difficult to correlate antifolate-induced toxicity with pretreatment folate levels. *Id*.

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

[15] We note that both Petitioner and Patent Owner addressed the two instituted grounds simultaneously, so we do the same in this Decision.

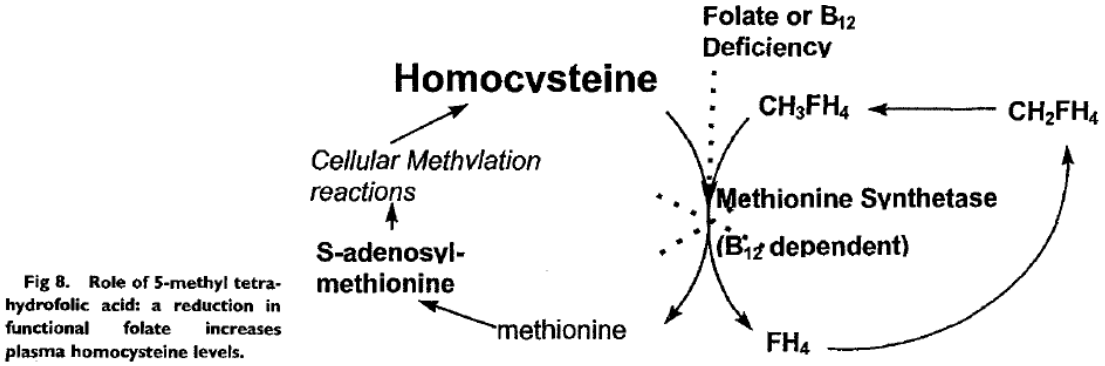


Fig 8. Role of 5-methyl tetrahydrofolic acid: a reduction in functional folate increases plasma homocysteine levels.

Id. at 9. As depicted in Figure 8 of Calvert, methionine synthase requires folate (5-methyltetrahydrofolate) as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction. According to Calvert, an increase in the plasma level of homocysteine occurs when there is a functional deficiency in either vitamin 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.

b. Niyikiza I (Ex. 1006)

Niyikiza I, a meeting abstract, states that MTA (pemetrexed) "is a novel multitargeted antifolate with inhibitory activity against multiple enzymes." Ex. 1006, 126, Abstract 609P. According to Niyikiza I, "[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 I 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 I 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 I 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 I states that further studies are underway in patients with renal impairment or patients who received prior cisplatin. *Id*.

c. EP 005 (Ex. 1033)

EP 005 is drawn to pharmaceutical preparations for lowering blood and tissue levels of homocysteine and counteracting harmful effects associated with homocysteine. Ex. 1033, 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 as vitamin 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. EP 005 teaches that

other situations in which blood homocysteine may be elevated include leukemia and other cancers. *Id.* at 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:

	PL		Folate		B12	
Formulation type	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 16.3 µmol/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 16.3 µmol/l. *Id.* at 17:28; *see also id.* at 12:42–45 (same).

d. The '974 patent (Ex. 1005)

The '974 patent describes the administration of a folate binding protein binding agent in conjunction with the use of an antifolate. Ex. 1005, 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 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 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.

e. Worzalla (Ex. 1013)

Worzalla looked at the "effects of folic acid on modulating the toxicity and antitumor efficacy of LY231514," the multitargeted antifolate

MTA. Ex. 1013, 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 3237–3238. 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*.

f. Hammond I (Ex. 1015)

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. 1015, 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.*

g. Niyikiza II (Ex. 1016)

Niyikiza II, a meeting abstract, considers the relationship of the metabolite profile in relation to the toxicity of pemetrexed. Ex. 1016, 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.*

h. Carrasco[16] (Ex. 1032)

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. 1032, 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 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

[16] Marina Carrasco et al., *Acute Megaloblastic Anemia: Homocysteine Levels Are Useful for Diagnosis and Follow-Up*, 84 HAEMATOLOGICA 767 (1999) (Ex. 1032) ("Carrasco").

> 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.

i. Hammond II[17] *(Ex. 1014)*

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. 1014, 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.*

j. 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 dose, as well as to look at its pharmacokinetic profile and potential antitumor activity. Ex. 2022, 489, Abstract 1559. Thirty-seven patients were treated

[17] 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. 1014) ("Hammond II").

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.*

k. Laohavinij[18] *(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 326–327. 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

[18] Sudsawat Laohavinij et al., *A Phase I Clinical Study of the Antipurine Antifolate Lometrexol (DDATHF) Given with Oral Folic Acid*, 14 INVESTIGATIONAL NEW DRUGS 325–335 (1996) (Ex. 2031) ("Laohavinij").

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.

l. Zervos[19] *(Ex. 2064)*

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. 2064, 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[20] *(Ex. 1052)*

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

[19] 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").

[20] 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. CLINICAL ONCOLOGY 1194 (1999) (Ex. 1052) ("Rusthoven").

initial chemotherapy for advanced non-small-cell lung cancer ("NSCLC"). Ex. 1052, 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.

n. Mendelsohn[21] (Ex. 1012)

Mendelsohn looked at the effects of dietary folate on the antitumor activity and toxicities of the antifolates lometrexol and LY309887, teaching that the preclinical profiles of the two antifolates are different, and that the two molecules appear to be clinically different. Ex. 1012, 262, 278. Mendelsohn teaches that in mice fed a low folate diet ("LFD") for two weeks, the toxicity of both lometrexol and LY309887 increased 300-1000 fold, and because of that lethality, the antitumor activity could not be

[21] Laurane G. Mendelsohn et al., *Preclinical and Clinical Evaluation of the Glycinamide Ribonucleotide Formyltransferase Inhibitors Lometrexol and LY309887*, *in* ANTIFOLATE DRUGS IN CANCER THERAPY 261 (Ann L. Jackman ed., 1999) (Ex. 1012) ("Mendelsohn").

determined. *Id.* at 269. Mendelsohn teaches, however, that oral supplementation with folic acid restored sensitivity to the antifolates, but that too high of a dose of folate eliminated both toxicity and antitumor activity. *Id.* at 269–270.

As to human patients, Mendelsohn teaches that the "folate status of cancer patients has not been systematically evaluated." *Id.* at 270. According to Mendelsohn, "dietary supplementation with folic acid may 'normalize' the dose response for achieving antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues having low folate requirements, without meeting the high folate demands of rapidly dividing tumor cells." *Id.*

Mendelsohn teaches:

> The biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B_{12} and B_6. Thus, the status of all three vitamins in patients may significantly influence the severity of toxicity observed during chemotherapy. R. Allen and his colleagues have established that measuring specific amino acid metabolites, especially homocysteine, N-methyl glycine and others, from these metabolic pathways provides a more sensitive and reliable assessment of patient vitamin status. These surrogate indicators of functional folate status are more indicative of deficiencies and more responsive to dietary supplementation.

Id. (reference omitted).

Mendelsohn looked at phase I studies of the antifolates both with and without folic acid supplementation. *Id.* at 272. According to Mendelsohn, "preclinical observations of the role of folic acid in preventing toxicity but preserving activity has been partially investigated in a clinical setting." *Id.* at 277. Mendelsohn teaches that although the trials were phase I trials, whereas efficacy is evaluated in a phase II trial, "it is encouraging to note

that a number of partial responses were observed in the phase I clinical development in those patients who received folic acid supplementation." *Id.*

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 grounds 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. 12. The folate pathway is involved in the synthesis of DNA and RNA precursors, and, interfering with that synthesis causes cell death or stasis. *Id.* Antifolates inhibit one or more enzymes in the folate pathway by binding to them in place of folate. PO Resp. 5. Because antifolates are known to inhibit folate dependent enzymes, they inhibit enzymes that are involved in the synthesis of DNA precursors. Pet. 9 (citing Ex. 1004 ¶ 28). Antifolates, however, exert their effects on all proliferating cells, not just cancer cells, and can cause severe side effects (i.e., toxicities). *Id.* 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. *Id.* at 11–12

c. Petitioner's Challenge

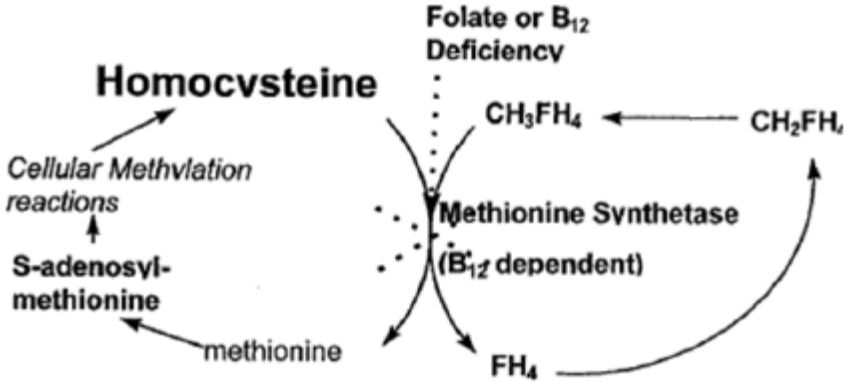
We start our analysis with independent claim 1, and note that the same analysis applies equally to independent claim 12, the only other independent claim challenged in this case. Claim 1 is drawn to a method of administering pemetrexed disodium, wherein an effective amount of folic acid and an effective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

Petitioner contends that the only difference between challenged claim 1 and Worzalla and Hammond I "is that the patients in Worzalla and Hammond I did not receive a methylmalonic acid ("MMA") lowering agent such as vitamin B_{12}." Pet. 27, 34; *see also id.* at 35–39 (claim chart). Petitioner asserts, however, that the ordinary artisan "would have recognized that administering vitamin B_{12} was the logical next step for reducing pemetrexed toxicity based upon the teachings of Calvert and Niyikiza I" in order to reduce pemetrexed toxicity. *Id.* 27–28.

In particular, Petitioner argues that Niyikiza I teaches that "[e]levated baseline homocysteine levels (≥10 μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA [pemetrexed]" and that Calvert summarizes Niyikiza I, stating that "any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine." Pet. 28 (quoting Ex. 1007, 8) (citing Ex. 1006, 126–127, Abstract 609P). Thus, Petitioner asserts, the ordinary artisan would have understood that the elevated homocysteine levels of Niyikiza were due to deficiencies in folic acid and/or vitamin B12, and that the ordinary artisan

would have understood that those homocysteine levels should be reduced by administering folic acid as taught by Worzalla and Hammond I, as well as through administering vitamin B12. *Id.* at 28–29 (citing Ex. 1020, Abstract; Ex. 1004 ¶¶ 74–79). That is, according to Petitioner, "[b]y pretreating with both folic acid and vitamin B_{12}, a POSA would address the underlying cause for the elevated homocysteine levels (a deficiency of folic acid, vitamin B_{12}, or both) and thus would reasonably expect that this pretreatment regimen would reduce the severity or prevalence of pemetrexed's toxicity." *Id.* at 29 (citing Ex. 1004 ¶¶ 66–79).

Petitioner contends further that the ordinary artisan would have understood that vitamin B12 was necessary to convert folic acid to its usable form, i.e., tetrahydrofolate or tetrrahydrofolic acd ("THF" or "FH_4"), which would have provided an additional reason to administer vitamin B12. *Id.* (citing Ex. 1004 ¶ 73). Petitioner relies on Figure 8 of Calvert to show that reaction, reproduced below:



Id. at 29–30. As shown in the above Figure, the folic acid derivative 5 methyl tetrahydrofolate ("CH_3FH_4") is converted to FH_4 through the action of the enzyme methionine synthase. *Id.* at 29.

Moreover, Petitioner argues, the ordinary artisan "would have also wanted to protect against overlooking a vitamin B_{12} deficiency." *Id.* at 30 (citing Ex. 1004 ¶¶ 83–86). According to Petitioner, it was "'well known' that it was 'inappropriate' to treat 'Cbl [cobalamin, a form of vitamin B12] deficiency with large doses of folic acid' because it could result in overlooking a hematologic response and deterioration of neurologic function – sometimes call B12-deficiency 'masking.'" *Id.* (quoting Ex. 1050, 95) (citing Ex. 1018, 7:51–54; Ex. 1039, 1931).

Petitioner asserts that to the extent that Niyikiza II "did not directly observe a correlation between pemetrexed toxicity and elevated MMA levels, which would indicate a vitamin B_{12} deficiency, the lack of such observation does not mean such a correlation does not exist." *Id.* at 31 (citing Ex. 1006, 126–127, Abstract 609P; Ex. 1016, 558a, Abstract 2139). According to Petitioner, as homocysteine and MMA are highly correlated, especially in patients with vitamin B12 deficiencies, "they may not be discerned as separate variables correlated with the outcome of pemetrexed toxicity." *Id.* (citing Ex. 1004 ¶ 80). Thus, Petitioner asserts, the ordinary artisan would have erred on the side of caution and also pretreated with vitamin B12 in the folic acid pretreatment regimen taught by Worzalla and Hammond I. *Id.* (citing Ex. 1029, Abstract; Ex. 1018, 7:51–54; Ex. 1004 ¶¶ 80–86). The ordinary artisan, Petitioner asserts, would have tested patients for elevated homocysteine, and for those patients having elevated homocysteine, would have tested for folic acid and vitamin B12 deficiencies, and would have pretreated those patients with vitamin B12 and folic acid deficiencies with vitamin B12 and folic acid, thus, meeting the elements of challenged claim 1. *Id.* at 31–32 (citing Ex. 1004 ¶¶ 80–86).

Moreover, Petitioner asserts, several prior art references teach administering vitamin B12 and folic acid to cancer patients. Pet. 32. Petitioner cites Carrasco for teaching treatment of a leukemia patient with methotrexate, wherein the toxicities associated with the methotrexate were ameliorated by administering vitamin B12 and folic acid. *Id.* (citing Ex. 1032, 767–768). Petitioner relies also on EP 005 as disclosing "that vitamin B_{12} may lower homocysteine levels resulting from 'any known cause' and that such causes include drugs such as the antifolate methotrexate." *Id.* (citing Ex. 1033, 4). Petitioner argues that it would have been obvious to pretreat with folic acid and vitamin B12 in view of the teachings of Calvert and Niyikiza I of the link between homocysteine levels and pemetrexed toxicity. *Id.* at 32–33 (citing Ex. 1006, 126–127, Abstract 609P; Ex. 1007, 8–9; Ex. 1004 ¶¶ 66–79). Petitioner further relies on Mendelsohn for its teaching that as the biochemical pathways that require folate cofactors also require vitamins B6 and B12, the status of all three may significantly affect toxicity. *Id.* at 33 (quoting Ex. 1012, 270).

Petitioner contends further that the ordinary artisan would have had a reasonable expectation of success of achieving the claimed invention. *Id.* at 39–44. Petitioner relies on Worzalla, Hammond I, and Hammond II asserting that those references teach that pretreatment with folic acid reduces toxicity, but still provides a therapeutic benefit. *Id.* at 40 (citing Ex. 1013, Abstract; Ex. 1015, 129Abstract 620P). Petitioner relies also upon the teachings of the '974 patent as confirming that it was known in the art that folic acid pretreatment reduces toxicity without destroying the therapeutic benefits of MTA. Pet. 40–41 (citing Ex. 1005, 1:47–58, 3:1–22).

Additionally, Petitioner argues that the prior art suggested that vitamin B12 may have anti-tumor effects, and, thus, also providing a reasonable expectation of success. *Id.* at 42 (citing Ex. 1023; Ex. 1026; Ex. 1027; Ex. 1028, 459A, Tisman Abstract). Petitioner relies on Arsenyan[22] as demonstrating "that when vitamin B_{12} was administered, either before or contemporaneously with the antifolate methotrexate, the mice had an increase in survival notwithstanding an initial transient increase in tumor size." *Id.* at 43 (citing Ex. 1023, 1300 (showing 21% increase in lifetime of animals pretreated with vitamin B12 and methotrexate); Ex. 1004 ¶ 88). In addition, Petitioner asserts, in a follow-up study, Sofyina,[23] the authors reported "additional tests showing a 'possible increase of the antitumor effect of MTX [methotrexate] with the use of methylcobalamine analogs and methionine synthase inhibitor.'" *Id*. (quoting Ex. 1026, 7 (alteration original)). Petitioner relies also on a study with 5FU demonstrating that folinic acid and folic acid can potentiate activity against different tumor cells. *Id.* (citing Ex. 1028, 459A, Tisman Abstract). Petitioner argues that the ordinary artisan would have understood that the transient increase in tumor size may have been due to the vitamin B12 and folic acid being stimulated into the DNA synthesis phase, which is the phase in which chemotherapeutic agents exert their effect. *Id.* (citing Ex. 1027, 301). Thus, the ordinary artisan would have understood, Petitioner avers, that the

[22] F.G. Arsenyan et al., *Influence of Methylcobalamin on the Antineoplastic Activity of Methotrexate*, 12 PHARMACEUTICAL CHEMISTRY J. 1299 (1978) (translation) (Ex. 1023) ("Arsenyan").

[23] Z.P. Sofyina et al., Possibility To Increase the Antitumor Effect of Folic Acid Antagonist with the Help of Methylcobalamine Analogs 72 (Sci. Ctr. of Oncology, 1979) (translation) (Ex. 1026) ("Sofyina").

vitamin B12 and folic acid could be used before administration of the chemotherapeutic agent, and would have expected vitamin B12 prtetreatment to have beneficial antitumor effects. *Id.* at 43–44 (citing Ex. 1027, 301; Ex. 1028, 459A, Tisman Abstract).

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.

Initially, we note that Petitioner in its Reply argues that we should discount the testimony Patent Owner's experts, Dr. Zeisel and Dr. Chabner. Reply 22. As to Dr. Zeisel, Petitioner argues that he is a nutritionist, and not a medical oncologist, and, thus, does not meet the qualifications of the ordinary artisan. *Id.* Dr. Chabner, Petitioner contends, did not testify from the standpoint of the ordinary artisan, rather, he assumed the ordinary artisan "would 'know[ ] everything I know.'" *Id.* In addition, Petitioner asserts that Dr. Chabner is biased, as he is good friends with Dr. Niyikiza, the inventor of the '209 patent, appreciates the presence of Lilly as an employer, has a long-standing consulting relationship with Lilly, and has friends at Lilly. *Id.* at 22–23. We take Petitioner's arguments into consideration as we consider Dr. Zeisel's and Dr. Chabner's opinions herein, and give them the appropriate weight in the context of the evidence of record.

As to Petitioner's assertion that it would have been obvious to pretreat with folic acid, 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. 5 (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 5–6.

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 20 (quoting Ex. 2020, 1398 (alteration in original); 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 (alteration in original); Ex. 2120 ¶ 65).

Moreover, Patent Owner contends that the ordinary artisan would have been concerned that pretreatment with folic acid would have enhanced 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[24] "observed that when children with acute leukemia were given injections of folic acid conjugates, the growth of the children's tumors accelerated." *Id.* at 20–21 (citing Ex. 1009, 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 Dr. Farber's work)). Patent Owner asserts that Petitioner's expert, Dr. Schiff, agreed that was a concern. *Id.* at 21 (citing Ex. 2026, 315).

Patent Owner asserts also that neither of Hammond I, Hammond II (collectively, "Hammond" or "the Hammond Abstracts"), Worzalla, or the '974 patent would give the ordinary artisan a reason to pretreat with folic acid. *Id.* at 23–34. According to Patent Owner, the ordinary artisan would not have viewed those references as a place to start in developing a dosing regimen for pemetrexed, rather, they confirmed that treatment with folic acid would have been harmful, thus, discouraging its use. *Id.* at 23–24 (citing Ex. 2120 ¶¶ 95, 169).

Hammond I and Hammond II, Patent Owner asserts, "report results from a Phase I clinical study of pemetrexed in which patients were pretreated with folic acid." *Id.* at 24. Patent Owner argues that even though a small level of minimal activity against cancer was seen in the presence of folic acid, the ordinary artisan would have still understood "that folic acid reduces efficacy and was therefore undesirable." *Id.* at 24–25. Patent Owner cites Rinaldi as teaching a Phase I clinical trial, similar to that in the

[24] 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. 1009) ("Farber").

Hammond Abstracts, in which no folic acid was administered. *Id.* at 25 (citing Ex. 2022, 489, Abstract 1559). Rinaldi, as Petitioner's expert, Dr. Schiff, acknowledged, "demonstrate[d] major anti-tumor responses." *Id.* (citing Ex. 2026, 184–189; Ex. 2022, 489, Abstract 1559; Ex. 2120 ¶¶ 52, 71–74; Ex. 1047, 36–37). The Hammond Abstracts, Patent Owner asserts, used higher doses of pemetrexed but had fewer responses. *Id.* (citing Ex. 1014, 225a, Abstract 866; Ex. 1015, 129, Abstract 620P; Ex. 2120 ¶¶ 71–74, 96). Thus, Patent Owner asserts, the ordinary artisan would have seen the protocols in the Hammond Abstracts as a failure. *Id.* (citing Ex. 2120 ¶¶ 33b, 75, 96).

According to Patent Owner, Petitioner argues in the Petition (Pet. 49–50) that Patent Owner is attempting to manufacture a teaching away by arguing that Rinaldi and the Hammond Abstracts are drawn to Phase I trials, and, thus, do not determine efficacy, to which Patent Owner responds that the ordinary artisan would have used those studies as indicators of efficacy. PO Resp. 26 (citing Ex. 2120 ¶¶ 72–75, 98–100). Patent Owner argues that "even if Hammond made a higher dose possible, that dose did not provide any efficacy advantage, and there was thus no reason to administer such a higher dose." *Id.* at 28 (citing Ex. 2120 ¶¶ 73–74). According to Patent Owner, Hammond teaches further that there was an increase in kidney toxicity with the higher doses of pemetrexed, thus, providing an additional reason to one of ordinary skill in the art to avoid pretreating with folic acid. *Id.* at 28–29 (citing Ex. 2120 ¶¶ 49, 76–82; Ex. 1015, 129, Abstract 620P; Ex. 1052, 1197–1198, Table 4; Ex. 2030).

Worzalla, Patent Owner asserts, also does not support pretreating with folic acid before administering pemetrexed. *Id.* at 29–30. Worzalla

implanted into mice "a special type of tumor engineered to be especially sensitive to antifolates," which would be particularly sensitive to the anti-cancer effects of pemetrexed. *Id.* at 30 (citing Ex. 2120 ¶ 156; Ex. 2026, 210–211). According to Patent Owner, the ordinary artisan would not use the results in that mouse model to "draw conclusions about how that regimen would affect the cancerous and normal cells of a human patient, which do not have this difference in sensitivity to antifolates." *Id.* at 30–31 (Ex. 2120 ¶ 156).

Moreover, Patent Owner asserts, Worzalla, like Hammond, confirms that folic acid pretreatment reduces the efficacy of pemetrexed. *Id.* at 31. Specifically, relying on Figure 2 of Worzalla, Patent Owner argues that "Worzalla showed that in the presence of folic acid, much more pemetrexed was needed to achieve the same effect as in mice that did not receive folic acid." *Id.* And although Worzalla expressly states that activity was preserved, albeit at higher doses, the ordinary artisan would not have followed that path in view of the data in Hammond that increasing the dose of pemetrexed "led to unacceptable kidney toxicity in humans." *Id.* at 32–33 (Ex. 2120 ¶ 161).

Patent Owner asserts also that the '974 patent does not help Petitioner. *Id.* at 33–34. According to Patent Owner, "[t]he '974 patent describes the administration of folic acid with the antifolate lometrexol to a single cancer patient, with precious little detail." *Id.* at 33 (citing Ex. 1005, 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.* at 33–34 (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 34 (citing Ex. 2120 ¶ 163).

Petitioner counters in its Reply that "Worzalla, Hammond, and the '974 patent expressly conclude that folic acid pretreatment preserved pemetrexed's efficacy while reducing its toxicity." Reply 2. In particular, Petitioner notes that Worzalla specifically teaches that folate intake can be manipulated so as to achieve greater therapeutic effect. *Id.* at 3 (citing Ex. 1013, 3238). Petitioner argues that Patent Owner is improperly focusing on only one half of the equation, which is, efficacy, and is ignoring "Worzalla's showing of a beneficial interplay between toxicity and efficacy resulting from folic acid pretreatment." *Id.* at 4.

As to the Hammond Abstracts, Petitioner contends that they expressly teach that pretreatment with folic acid allows dose escalation of pemetrexed by ameliorating its toxicity. *Id.* at 5 (citing Ex. 1015, 129, Abstract 620P; Ex. 1014, 225a, Abstract 866; Ex. 1083, 371). Patent Owner's argument that Hammond did not show efficacy, Petitioner asserts, turns "Hammond into something it's not: a study on efficacy." *Id.* (citing Ex. 1075 ¶ 41). As conceded by Patent Owner's expert, Dr. Chabner, Petitioner argues that variables that have nothing to do with the drug under investigation can impact the efficacy of Phase I trials. *Id.* at 5–6 (citing Ex. 1074, 52:16–53:22; Ex. 1075 ¶¶ 39, 44). Petitioner asserts, therefore, "the partial response reported in Hammond II would be viewed as encouraging, but could not be used to quantify efficacy." *Id.* at 6 (citing Ex. 1075 ¶¶ 35, 37).

Petitioner argues further that Patent Owner's comparison of the Hammond Abstract to other studies, such as those of Rinaldi and Rusthoven, are flawed. *Id.* (citing Ex. 1075 ¶¶ 36–49). For example, Petitioner asserts that the lack of major anti-tumor response in Hammond does not teach away from pretreating with folic acid. Rather, according to Petitioner, the ordinary artisan would have understood that there was some antitumor response shown despite the prognosis of the participants. *Id.* (citing PO Resp. 27; Ex. 1075 ¶ 37). In addition, Petitioner argues also that Hammond does not express any concern about toxicity to the kidneys. *Id.* at 7 (citing Ex. 1075 ¶¶ 50–53; 58–59; Ex. 1100, 2331; PO Resp. 26–29). Laohavinij, Petitioner asserts, rather than supporting Patent Owner's contention that one would not pretreat with folic acid, actually supports such pretreatment. *Id.* (citing Ex. 2031, 333–334; Ex. 1074, 99:24–100:5).

As to the '974 patent, Petitioner argues that Patent Owner's arguments that the patent has no data and little detail fails to take into account that it has three columns of animal data, as well as a report on pilot studies in humans. *Id.* at 8 (citing Ex. 1005, 6:57–8:47; 8:49–58; Ex. 1075 ¶¶ 60–64). In addition, Petitioner asserts, Patent Owner listed the '974 patent in the FDA's Orange Book as covering pemetrexed. *Id.* (citing Ex. 1025, 145).

Petitioner asserts further that the ordinary artisan would have had a reasonable expectation of success of pretreating with folic acid to reduce pemetrexed's toxicities. *Id.* at 17–19. Specifically, Petitioner asserts that "Worzalla, Hammond, and the '974 patent's plain statements about the benefits of folic acid pretreatment would have provided [an ordinary artisan] with a reasonable expectation of success in using folic acid pretreatment with pemetrexed." *Id.* at 17. Petitioner asserts that all of Patent Owner's

concerns about efficacy "stem almost entirely from Lilly's flawed reading of a couple of sentences in an article by Laohavinij that concerns another antifolate, lometrexol." *Id.* (citing Ex. 2120 ¶¶ 66–68, 96, 100, 166, 197, 200, 221; Ex. 2031, 333; Ex. 1075 ¶¶ 45–46). Laohavinij, Petitioner contends was a Phase I study and, thus, its objectives did not include efficacy. *Id.* Laohavinij did, however, reference two previous studies that noted folic acid reduced toxicity but not efficacy. *Id.* (citing Ex. 2031, 326 (refs. 10–11); Ex. 1011, 324, Abstract 1921; Ex. 1090, 2331 (ref. 16)). Moreover, Petitioner asserts, Laohavinij relies on a 1948 paper by Dr. Farber that concerns a different folate and a different mechanism of action. *Id.* at 18 (citing Ex. 1009, 787, 792; Ex. 1091 ¶ 17; Ex. 1075 ¶¶ 95–96). The ordinary artisan, Petitioner asserts, would have looked at later studies such as Worzalla and Hammond that evidence that pretreatment with folic acid would reduce the toxicity of pemetrexed while preserving its efficacy. *Id.* (citing Ex. 1074, 179:5–10; Ex. 1075 ¶¶ 34, 86, 95–96).

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 Petitioner's contention 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 disodium. That is, we find 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 describes the administration of folic acid to a patient before the administration of an antifolate. Ex. 1005, Abstract, 1:54–58, 2:60–3:22. In addition, Worzalla teaches that supplementation with folic acid preserved the antitumor activity of MTA, that is, pemetrexed, while reducing its toxicity. Ex. 1013, Abstract. Hammond I teaches folic acid supplementation before the administration of MTA appears to permit dose escalation of the MTA by ameliorating toxicity (Ex. 1015, 129, Abstract 620P), and Hammond II also teaches that folic acid supplementation appears to permit pemetrexed dose elevation (Ex. 1014, 225a, Abstract 866). 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 in 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, suggest pretreatment with folic acid before administration of an antifolate, such as MTA, and are, thus, addressing the toxicity associated with the administration of the antifolate, and balancing it with the efficacy of the antifolate. That finding is supported by the prior art. For example, Grindey[25] teaches that in C3H mice, "[h]igh doses of folic acid in the drinking water completely reverse both toxicity and activity" of lometrexol, whereas "low doses of folic acid . . . prevent this dietary-induced toxicity and >90% inhibition of tumor growth is achieved." Ex. 1011, 324, Abstract 1921. Thus, Grindey suggests that the efficacy of the antifolate, in this case, lometrexol, needs to be balanced with managing its toxicity. In addition, Mendelsohn teaches that oral supplementation with folic acid restored sensitivity to the antifolates lometrexol and LY309887, but that too high of a dose of folate eliminated both toxicity and antitumor activity. Ex. 1012, 269–270. Thus, Mendelsohn suggests also that the efficacy of the antifolate needs to be balanced with managing its toxicity.

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

[25] G.B. Grindey, et al., *Reversal of the Toxicity But Not the Antitumor Activity of Lometrexol by Folic Acid*, 32 PROC. OF THE AM. ASS'N CANCER RES., Mar. 1991, at 324, Abstract 1921 (Ex. 1011) ("Grindey").

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. 19–21), Patent Owner's counsel acknowledged that folic acid pretreatment would not completely eliminate pemetrexed's effectiveness (Tr. 78:15–80:6).

We have also carefully considered Patent Owner's arguments regarding Farber (Ex. 1009), but do not find them persuasive. Dr. 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 the their authors would have presumably been aware of that work. *See*, *e.g.*, *GPAC*, 57 F.3d at 1573 (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. 20–21), Laohavinij specifically cites Dr. Farber's work. Ex. 2031, 333 & n.35 (citing Farber).

We have also considered Patent Owner's arguments as to the '974 patent. 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, e.g.*, 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 Worzalla, Hammond I, Hammond II, and Laohavinij also suggest pretreatment with folic acid before administering an antifolate, and Worzalla, Hammond I, and Hammond II specifically teach the antifolate required by the challenged claims—pemetrexed. 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.

We also do not find persuasive Patent Owner's contention (PO Resp. 28–29) that Hammond I provides an additional reason to one of ordinary skill in the art to avoid pretreating with folic acid by teaching further that there was an increase in kidney toxicity with the higher doses of pemetrexed. Hammond I did not categorize creatinine clearance, which is indicative of kidney toxicity (*see* Ex. 2120 ¶¶ 78), as a major toxicity, but rather as Grade 1 or 2 toxicity. Ex. 1015, 129, Abstract 620P. In addition, Hammond I expressly concludes that "[folic acid] supplementation appears to permit MTA dose escalation by ameliorating toxicity" (*id.*) and, therefore, does not appear to consider kidney toxicity an impediment to pretreating with folic acid.

According to Patent Owner, at the time of invention, the general understanding was that the toxicities associated with the administration of pemetrexed were manageable by conventional means, and, thus, the ordinary artisan would not have looked at means of managing those toxicities, such as through the pretreatment with folic acid, which could potentially have a large and unpredictable effect on the efficacy of the antifolate. *Id.* at 21–22 (citing Ex. 2120 ¶¶ 33a, 33b, 53–61, 82, 91–92 144–147; Ex. 1045, 107; Ex. 1052, 1194, 1198). 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 22–23 (citing Ex. 2120 ¶¶ 57, 61, 63, 66–67, 151; Ex. 1014, 225a, Abstract 866; Ex. 1015, 129, Abstract 620P; Ex. 1052, 1198).

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 toxicities. Reply 15–16. According to Petitioner, the prior art taught that there was a high incidence of Grade III and Grade IV toxicities, and Patent Owner's expert, Dr. Chabner, admitted that such toxicities would be dangerous. *Id.* at 15 (citing Ex. 1074, 223:14–224:5, 224:23–225:3; 254:10–13; Ex. 1075 ¶¶ 12–20; Ex. 1070, 339a, Abstract 1307). Petitioner argues that, in fact, Patent Owner's own article, Rusthoven, "suggests folic acid pretreatment to reduce so-called 'tolerable' pemetrexed-related toxicity." *Id.* (citing Ex. 1052, 1198).

Petitioner contends that the alternatives proposed by Patent Owner are impractical, and relies on the Declaration of its expert, Dr. Schiff, who states that the alternatives do not address "the full breadth of pemetrexed's

toxicities, were unknown for chemotherapy, required cumbersome administration, or would have negatively impacted efficacy." *Id.* at 16 (citing Ex. 1075 ¶¶ 21–33; Ex. 1072, 14; Ex. 2033, 2805; Ex. 1086, 38:12–39:9; Ex. 1097; Ex. 1091 ¶¶ 32–35; Ex. 1074, 261:1–262:6, 267:16–25; 276:24–277:25, 278:4–14). Moreover, Petitioner asserts, the fact that there may be alternatives is not a teaching away. *Id.*

We do not find Patent Owner's arguments and evidence to be persuasive in this regard. "[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) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)). 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 an antifolate, such as 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.

Patent Owner disagrees with the argument made in the Petition that it would have been obvious to pretreat with vitamin B12 in addition to folic acid before administering pemetrexed on the basis of the elevated homocysteine levels seen by Niyikiza. Specifically, Patent Owner 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. 7 (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.* at 8. According to Patent Owner, elevated levels of MMA may be indicative of a vitamin B12 deficiency, but folic acid deficiencies do not lead to elevated MMA levels. *Id.* (citing Ex. 2120 ¶ 40; Ex. 2118 ¶ 43). Thus, Patent Owner asserts, "if a patient ha[s] elevated homocysteine levels but d[oes] not have elevated MMA levels, this indicates that they have a folate deficiency but not a vitamin B_{12} deficiency." *Id.*

According to Patent Owner, Dr. Niyikiza endeavored to determine those patients that would be most likely to develop toxicities from pemetrexed, and published his results in Niyikiza I (Ex. 1006, 126–127, Abstract 609P) and Niyikiza II (Ex. 1016, 558a, Abstract 2139). PO Resp. 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 "found no such correlation between pemetrexed toxicity and MMA levels." *Id.* (citing Ex. 1016, 558a, Abstract 2139; Ex. 2120 ¶¶ 33d, 106; Ex. 2118 ¶ 70); *see also id.* at 40–41 (same). Patent Owner argues that finding indicates that there is not a correlation between pemetrexed toxicity and the

patient's vitamin B12 levels. *Id.* at 10 (citing Ex. 2120 ¶¶ 33d, 106; Ex. 2118 ¶ 70); *see also id.* at 40 (same). That is, Patent Owner asserts, the ordinary artisan would have understood that "there was no correlation between a vitamin B_{12} deficiency and pemetrexed-induced toxicity," and that "the patients experiencing an elevated risk of toxicities did *not* have a vitamin B_{12} deficiency." *Id.* at 40 (citing Ex. 2120 ¶¶ 106–107; Ex. 2118 ¶ 43).

Patent Owner asserts further as to the Niyikiza Abstracts, as well as Calvert, which reported Niyikiza's work, that, as Dr. Schiff admitted, the ordinary artisan would have understood that pemetrexed was causing the toxicity, not elevated homocysteine levels. *Id.* at 37–38 (citing Ex. 2026, 116; Ex. 2120 ¶¶ 113–115). According to Patent Owner, although Niyikiza suggests that there is a correlation between pemetrexed toxicities and elevated homocysteine levels, Niyikiza does not suggest that homocysteine is a cause of the toxicity, or that lowering homocysteine would have led to a reduction in toxicity. *Id.* at 38 (citing Ex. 1006, 126–127, Abstract 609P; Ex. 1016, 558a, Abstract 2129; Ex. 2120 ¶¶ 104–113). In fact, Patent Owner asserts, Niyikiza expressly teaches that homocysteine levels did not appear to change from baseline during treatment with pemetrexed, and the toxicities reported by Niyikiza were pemetrexed toxicities, not homocysteine toxicities. *Id.* (citing Ex. 1006, 126–127, Abstract 609P; Ex. 1016, 558a, Abstract 2129; Ex. 2120 ¶¶ 109, 113). Patent Owner argues also that the baseline homocysteine levels reported by Niyikiza that correlated with increased toxicities with pemetrexed treatment, were not, by themselves, abnormally high, so would not warrant treatment *per se*. *Id.* (citing Ex. 2026, 121–122; Ex. 2120 ¶ 117; Ex. 2118 ¶ ¶ 63–65). Calvert does not add

anything, Patent Owner asserts, as it is only reporting Niyikiza's work. *Id.* at 39 (citing Ex. 2120 ¶¶ 141–142). And Calvert does not teach or suggest that folic acid and vitamin B12 pretreatment should be used, as Dr. Schiff admitted. *Id.* (citing Ex. 2026, 167).

In response to the argument in the Petition (Pet. 31) that the lack of an observation between MMA levels and pemetrexed toxicity does not mean that such a correlation does not exist, Patent Owner argues that is not how obviousness works, as at least one reference must provide a reason to combine the references to arrive at the claimed invention. *Id.* at 41. Petitioner's argument that the ordinary artisan would have erred on the side of caution and pretreated with vitamin B12, Patent Owner asserts, is impermissible hindsight. *Id.* Patent Owner asserts further that even if the ordinary artisan would have been motivated to lower homocysteine, there were other known ways to do it, such as supplementation with betaine that would not reduce the efficacy of the pemetrexed. *Id.* at 41–42 (citing Ex. 2033, 2805; Ex. 2120 ¶¶ 33d, 130–132; Ex. 2118 ¶ 75).

In addition, Patent Owner contends that EP 005 also would not have suggested to the ordinary artisan to pretreat with folic acid and vitamin B12. *Id.* at 42. Patent Owner argues that EP 005 is not an oncology reference, but focuses on lowering homocysteine to aid in the prevention of cardiovascular disease. *Id.* (citing Ex. 2118 ¶¶ 73–74; Ex. 2120 ¶¶ 133–134). 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.* at 43 (citing Ex. 2120 ¶ 135). Thus, Patent Owner avers, EP 005 only provides

a reason to treat with folic acid and vitamin B12 if lowering homocysteine levels is the only goal. *Id.*

Patent Owner argues that Petitioner further 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 in passing that methotrexate may increase homocysteine levels. *Id.* (citing Pet. 32; Ex. 1033, 4). Niyikiza, however, reported that pemetrexed did not increase homocysteine levels, and, thus, Patent Owner asserts the teaching regarding methotrexate in EP 005 is irrelevant to Niyikiza. *Id.* (citing Ex. 2120 ¶ 138). In fact, Patent Owner contends, there is no indication that EP 005 ever used its regimen in cancer patients. *Id.* at 43–44 (citing Ex. 2120 ¶¶ 63–64, 133–140; Ex. 2020, 1398; Ex. 2025, 1282; Ex. 2026, 176–179).

Patent Owner argues also that "vitamin B_{12} pretreatment of an antifolate cancer patient is nowhere to be found in any of the references that [Petitioner] cites" and "was totally unprecedented as part of an antifolate chemotherapy regimen." PO Resp. 1–2, 34 (citing Ex. 2120 ¶¶ 83–85, 97, 102–103, 162, 168, 193). Patent Owner asserts that Petitioner's expert, Dr. Schiff, "admitted that he was not aware of anyone using vitamin B_{12} pretreatment in a cancer patient receiving antifolate therapy." *Id.* at 35 (citing Ex. 2026, 111, 273–274). Patent Owner does note, however, that Dr. Schiff tries to characterize 5-fluorouracil as an antifolate. According to Patent Owner, however, even though 5-fluorouracil does inhibit an enzyme in the folate pathway, it is not an antifolate as it does not compete directly with folate *Id.* at 35 n.4 (citing Ex. 2120 ¶¶ 172–178).

Patent Owner argues that vitamin B12 "can also interfere with an antifolate's anti-cancer efficacy by increasing folate levels." *Id.* at 6, 35

(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, and that active form may then be used to make DNA precursors. *Id*. at 6. The enzyme methionine synthase, which requires vitamin B12, Patent Owner asserts, 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.* (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.* at 6–7 (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 administering a folate, because administering vitamin B_{12} could convert a large pool of 'trapped' folate into its active form." *Id.* at 7 (citing Ex. 2120 ¶¶ 52–56; Ex. 2118 ¶¶ 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.* (citing Ex. 2120 ¶¶ 33c, 39, 85–87, 102–103, 123, 206; Ex. 2118 ¶¶ 52–56).

Moreover, Patent Owner argues that the ordinary artisan would not have been concerned about a masked vitamin B12 deficiency in cancer patients. *Id.* at 44 (citing Pet. 30–31). According to Patent Owner, "'[m]asking' arises only in patients who are presenting with clinical

manifestations of a vitamin deficiency and who are administered folate to treat that deficiency." *Id.* (citing Ex. 2120 ¶ 190; Ex. 2118 ¶ 77). Patent Owner argues that the risk of masking is low, asserting that clinical vitamin B12 deficiencies are rare. *Id.* at 45 (citing Ex. 2118 ¶ 78; Ex. 2120 ¶ 196). And, "even if masking were a real concern, the neurotoxicity that vitamin B_{12} deficiency can cause progresses so slowly—measured in terms of years—that the [ordinary artisan] would have seen no reason to pretreat with vitamin B_{12}, since any neuropathy (for which cancer patients are monitored in any event) could be safely treated after cancer therapy is completed." *Id.* (citing Ex. 2118 ¶ 77; Ex. 2120 ¶ 195).

Patent Owner asserts additionally that Petitioner's arguments "are belied by the very precedent it cites," as "[b]oth Hammond and Laohavinij administered folic acid to cancer patients; neither so much as mentions vitamin B_{12}." *Id.* (citing Ex. 2120 ¶¶ 191–192). In addition, Petitioner's expert, Dr. Schiff acknowledged that vitamin B12 is not typically administered with folate in the context of folate rescue therapy. *Id.* at 45–46 (citing Ex. 2026, 25; Ex. 2120 ¶ 193).

Petitioner responds that Niyikiza teaches that there is a correlation between pretreatment homocysteine levels and the toxicity of pemetrexed, and Calvert teaches that elevated homocysteine levels may be caused by both folic acid and vitamin B12 deficiencies. Reply 10 (citing PO Resp. 37; Ex. 1074, 150:12–16, 161:1–164:3). Thus, according to Petitioner, none of Patent Owner's arguments undercut the rationale in the Petition that the ordinary artisan "would have been motivated to add vitamin B_{12} to the known folic acid pretreatment regimen of Worzalla and Hammond I and in doing so, the [ordinary artisan] would have had a reasonable expectation that

both the patient's homocysteine level would be reduced and pemetrexed-related toxicities would be reduced." *Id.*

Petitioner contends that Patent Owner's "distinction between the correlation of homocysteine levels and pemetrexed toxicity and causation of this toxicity deliberately misses the point." *Id.* at 11 (citing PO Resp. 38; Ex. 1075 ¶ 68). According to Petitioner, as Patent Owner's expert, Dr. Zeisel testified, what the ordinary artisan would have taken from Niyikiza was that "there might be something about having a higher level than 10 [μM homocysteine] that was related to why people were getting toxicity from pemetrexed." *Id.* (quoting Ex. 1086, 29:7–12). Petitioner asserts that Calvert indicates that those elevated homocysteine levels indicate a functional folate deficiency, and the ordinary artisan would have understood that was a cause of pemetrexed toxicity. *Id.* (citing Ex. 1075 ¶¶ 74–75). As the claims do not require a particular physiological basis, Petitioner argues that it is irrelevant whether it is the elevated homocysteine levels or the functional folate deficiency that cause the pemetrexed toxicity. *Id.* (citing Ex. 1075 ¶ 68; Ex. 1091 ¶ 41). And as it was well known by June of 1999 that "pretreating with folic acid and vitamin B_{12} (low levels of which are common causes of elevated homocysteine) would reduce pretreatment homocysteine levels and the [ordinary artisan] would have appreciated that the resulting reduced homocysteine correlated with reduced pemetrexed toxicity." *Id.* at 11–12.

Petitioner asserts further that "Lilly's expert, Dr. Bruce Chabner, admitted that it was known prior to June 1999 that folic acid and vitamin B_{12} pretreatment would decrease pemetrexed's toxicity." *Id.* at 1 (citing Ex. 1074, 88:12–18, 89:14–22). Petitioner asserts, therefore, that Patent Owner

is "demand[ing] more than what obviousness requires when it complains that Niyikiza 'does not make any recommendations' on how to lower homocysteine and that Calvert 'makes no suggestion as to how the [ordinary artisan] should use the information'" of Niyikiza. *Id.* at 12.

Petitioner argues further that Niyikiza II did not find that MMA levels were not correlated with pemetrexed toxicity, rather, "Niyikiza II merely notes that no such correlation '***was seen***.'" *Id.* (citing Ex. 1016, 558a, Abstract 2129; PO Resp. 40). Petitioner cites its expert, Dr. Schiff, as well as the testimony of Patent Owner's experts, Drs. Chabner and Zeisel, to support the proposition that just because Niyikiza did not see a correlation does "not exclude the possibility that it exits." *Id.* at 12–13 (citing Ex. 1075 ¶¶ 65–73; Ex. 1074, 153:7–13; 153:24–154:1; Ex. 1086, 116:19–20; Ex. 1091 ¶ 42). That is, Petitioner asserts, "[b]ecause MMA and homocysteine were known to be highly correlated to one another, no conclusions can be drawn based on lack of data showing a correlation." *Id.* at 13 (citing Ex. 1004 ¶ 80; Ex. 2026,[26] 126:22–130:15; Ex. 1074, 157:23–158:2). In fact, Petitioner avers, Patent Owner explained to the FDA "that the 'B12 deficiency marker, methylmalonic acid, was highly correlated with homocysteine and was therefore removed from the initial multivariate analysis conducted in 1998 to eliminate issues of collinearity.'" *Id.* (quoting Ex. 1088,[27] 3).

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[26] We note that the Reply cites Exhibit 2126. Exhibit 2126 (Deposition Transcript of Dr. Schiff), however, is not part of the record. *See* Paper 73 (Patent Owner's Updated Exhibit List). We, therefore, assume that Petitioner is referring to Exhibit 2026 (Schiff Deposition Transcript).

[27] Eli Lilly & Co., LY231514 (ALIMTA): Impact of Folic Acid and Vitamin B12 Supplementation on Safety (June 4, 2001) (Ex. 1088).

In addition, Petitioner asserts, the reason to add vitamin B12 was not a possible correlation between vitamin B12 and toxicity, but that Niyikiza I taught that homocysteine levels were correlated to toxicity and the ordinary artisan, as supported by Calvert and EP 005, would have understood that folic acid and vitamin B12 together would reduce homocysteine. *Id.* Specifically, as to EP 005, Petitioner asserts that Patent Owner does not dispute that methotrexate, another antifolate, increases homocysteine levels, or that EP 005 teaches that blood homocysteine levels may be controlled by a combination of folic acid and vitamin B12. *Id.* at 13–14 (citing Ex. 1033, 4, 11; Ex. 1074, 185:24–186:7; Ex. 1075 ¶ 77). Petitioner argues that Patent Owner attempts to dismiss that teaching by EP 005 as irrelevant because pemetrexed does not increase homocysteine as methotrexate does, but, Petitioner argues, "EP005 broadly teaches administering folic acid and vitamin B_{12} to lower homocysteine regardless of cause." *Id.* at 14 (citing Ex. 1033, 4; Ex. 1075 ¶¶ 77, 79–80). Patent Owner is ignoring the teachings of Niyikiza, Petitioner asserts, when it argues that EP 005 does not provide a reason to pretreat with folic acid and vitamin B12 in the context of pemetrexed chemotherapy, as Niyikiza explicitly teaches that elevated baseline levels of homocysteine are predictive of pemetrexed toxicity. *Id.* (citing Ex. 1016; Ex. 1075 ¶ 78).

Petitioner asserts furthermore that the ordinary artisan would have no concerns about pretreating with vitamin B12 before administering pemetrexed. *Id.* at 19–20. As to issues with a methyl trap, Petitioner argues "[t]o the extent any such concern ever existed, it was debunked for pemetrexed by Worzalla and Hammond – prior to June 1999." *Id.* at 19 (citing Ex. 1075 ¶ 34). Moreover, to the extent that the ordinary artisan

would not have been worried about masking, Petitioner asserts, they would have also not been worried about a methyl trap. *Id.* (citing Ex. 1091 ¶¶ 25–31; Ex. 1075 ¶ 98). And to the extent that the methyl trap was a concern, Petitioner contends, that provided a further reason to pretreat with vitamin B12 as well as folic acid "to ***prevent*** potentially masking the type of profound B_{12} deficiency that might cause devastating neurological damage – or lead to a methyl-trap scenario." *Id.* at 20 (citing Ex. 1075 ¶¶ 82–85; Ex. 1091 ¶¶ 36–40; Ex. 1087, 125).

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 although the evidence of record may support pretreatment with folic acid before administration of pemetrexed disodium, it does not support pretreatment with a methylmalonic acid lowering agent, such as vitamin B12, as well. In that regard, we find that the preponderance of the evidence of record supports the finding that if a patient is deficient in vitamin B12, that patient would have elevated levels of both homocysteine and MMA. That finding is supported by the testimony of Petitioner's expert, Dr. Schiff:

> 11 Q. And in the -- for homocysteine, in the
> 12 absence of further information, if you knew a person
> 13 had elevated homocysteine, it could either be a
> 14 folate deficiency or a vitamin B12 deficiency or
> 15 potentially other things, correct?
> 16 A. Yes. Or both folic acid and vitamin
> 17 B12.
> 18 Q. Right. But methylmalonic acid elevation
> 19 is not associated with folate deficiency; it's only
> 20 associated with vitamin B12 deficiency.

21 A. That's correct.

Ex. 2026, 126:11–21.

The fact that deficiencies in both vitamin B12 and folate can lead to elevated homocysteine levels, but elevated MMA levels are indicative of a vitamin B12 deficiency but not a folate deficiency, is supported also by the prior art. For example, Savage, which was relied upon by Dr. Chabner in his Declaration (Ex. 2120 ¶ 40), teaches that out of "434 episodes of cobalamin [vitamin B_{12}] deficiency," 98.4 % patients had elevated MMA levels and 95.9% had elevated homocysteine levels. Ex. 2039, Abstract. As for the 123 patients with folate deficiency, homocysteine levels were elevated in 91% of the patients, whereas MMA levels were elevated in only 12.2% of the patients, and in all but one, "the elevation was attributable to renal insufficiency or hypovolemia." *Id.*, *see also id.* at Table VII (showing that serum MMA is raised 98.3% of the time in patients with vitamin B12 deficiency, but only 4.1% of the time in patients with pure folate deficiency). In addition, Carrasco, relied upon by Petitioner, teaches also that in vitamin B12 deficiencies both homocysteine and methylmalonic acid levels are high, whereas in folate deficiencies, only homocysteine levels are increased. Ex. 1032, 768.

As noted by Patent Owner, (PO Resp. 10), Niyikiza, which looked at both homocysteine and MMA levels, stated that "[s]tepwise regression modeling, 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. 1006, 126–127, Abstract 609P. Although teaching that "[*t*]*oxicities resulting from treatment with MTA appear to be* predictable from pretreatment homocysteine levels,"

Niyikiza teaches that homocysteine levels "did not appear to change from baseline during treatment with MTA." *Id*. Importantly, although Niyikiza looked at MMA plasma levels, Niyikiza does not state that MMA levels were correlated with toxicity, or that they changed during treatment.

Niyikiza II reports similar results. Nyikiza 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. 1016, 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 was seen." *Id*. Again, Niyikiza II does not state 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 prespecified 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.

We do not find persuasive Petitioner's argument that just because a correlation was not seen, that does not mean such a correlation does not exist. In that regard, we recognize that Petitioner's expert, Dr. Schiff, testifies:

> Dr. Chabner also misses the fact that Niyikiza II does not affirmatively state that there was no correlation between MMA and toxicity, but instead notes that no correlation "was seen," leaving open the possibility that a correlation might later be seen via further studies. By contrast, Niyikiza II affirmatively states that "[c]ystathionine levels did ***not*** correlate . . . ." (Ex. 1016, Niyikiza II (emphasis added).)

Ex. 1075 ¶ 66. We do not find the fact that Niyikiza II affirmatively stated that cystathione levels did not correlate with hematologic toxicity or mucositis to support the inference that MMA levels may correlate to toxicity. For example, the statement in Niyikiza II that "[t]here was a strong correlation between baseline homocysteine levels and the development of the following toxicities . . ." would support the opposite inference. Ex. 1016, 558a, Abstract 2139. But as Niyikiza II specifically states that it measured MMA levels, and that "[n]o correlation between toxicity . . . and the remaining pre-specified predictors was seen" (*id.*), we find that Dr. Chabner's testimony, reproduced above, best reflects the teachings of that reference. *See* Ex. 2120 ¶ 106.

Moreover, in arguing the fact that Niyikiza II did not see a correlation between MMA levels and pemetrexed toxicity does not mean that such a

correlation does not exist, Petitioner engages in speculation. In that regard, we agree with Patent Owner (PO Resp. 41) that is not how obviousness works, as after reading the references, there must be a reason to combine the references to arrive at the claimed invention. Thus, as Niyikiza II does not teach an increase in MMA levels during administration of pemetrexed, and in fact, does not even teach that there is a correlation of MMA levels with pemetrexed toxicity, Niyikiza II does not supply a reason to lower those levels by pretreatment with an MMA lowering agent, such as vitamin B12, 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 normal levels of methylmalonic acid. Ex. 2064, 256a, Abstract 907. Thus, this reference, like other prior art cited, does not provide a sufficient reason to administer a MMA lowering agent, such as vitamin B12, when administering pemetrexed.

In addition, Calvert does not provide an independent reason to pretreat with vitamin B12 as well as folic acid. As Petitioner notes (Pet. 28, Reply 10), Calvert does teach that "any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine," noting that the "measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA." Ex. 1007, 8–9 (citing Niyikiza II)). But as discussed above, we find that the evidence of record supports the finding that if a patient is deficient in vitamin B12, that patient would have elevated levels of both homocysteine and MMA. As Niyikiza II does not teach elevated MMA levels are associated with pemetrexed, the

ordinary artisan would not have had a reason to also pretreat a cancer patient with vitamin B12 before the administration of pemetrexed.

In addition, Petitioner, in its Reply, contends that "Lilly's expert, Dr. Bruce Chabner, admitted that it was known prior to June 1999 that folic acid and vitamin B12 pretreatment would decrease pemetrexed's toxicity." *Id.* at 1 (citing Ex. 1074, 88:12–18, 89:14–22). In fact, Dr. Chabner testified the following:

> 16 Would a person of ordinary skill in the art,
> 17 as of June of 1999, have a reasonable expectation
> 18 that pretreatment with Vitamin B12 would reduce
> 19 the toxicity of an antifolate on normal cells?
> 20 A. Yes, it could. It would depend on the
> 21 circumstances, though. I would -- can I qualify
> 22 my answer?
> 23 Q. You're the witness
> 24 A. Okay
> 25 Q. All right.
> 1 A. So the witness would say that it would
> 2 depend on the status of the folates in -- I think
> 3 it would -- if a person were B12 deficient, it
> 4 certainly would. If a person were B12 replete,
> 5 it might not -- might have very little effect.
> 6 And the reason I say that is the folate pools,
> 7 the reduced folate pools would then be, in that
> 8 person, may be fully adequate to -- to deal with
> 9 the drug in the normal cells. But we wouldn't
> 10 know. You'd have to try it. I think it has the
> 11 potential of reducing toxicity in the patient
> 12 that has B12 deficiency. But, as I said, it also
> 13 has the potential of reversing the antitumor
> 14 activity.

Ex. 1074, 90:16–91:14.

Thus, Dr. Chabner testified that the ordinary artisan may have thought pretreatment with vitamin B12 would have alleviated pemetrexed toxicity if

the patient was determined to be vitamin B12 deficient. As discussed in regard to Niyikiza and other references, however, Petitioner does not point to sufficient evidence demonstrating that cancer patients treated with pemetrexed, who exhibited increased homocysteine levels, would have been vitamin B12 deficient.

Furthermore, Petitioner does not cite to persuasive evidence to support a finding of synergistic benefits of using vitamin B12 with folic acid where there is no indication that a patient is vitamin B12 deficient, as in Niyikiza II. Reply 14 (citing Ex. 1033, 11:20–25). Although Petitioner cites EP 005 as teaching synergistic benefits, as Petitioner's counsel clarified, EP 005 and other 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 finding that the ordinary artisan would have expected to achieve the synergistic benefits taught in EP 005 in the specific instance where a patient does not have low levels of vitamin B12.

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. According to Petitioner, "EP005 broadly teaches administering folic acid and vitamin B_{12} to lower homocysteine regardless of cause," and Patent Owner does not dispute that methotrexate, another antifolate, increases homocysteine levels, and also teaches that blood homocysteine levels may be controlled by a combination of folic acid and vitamin B12. Reply 13–14.

We recognize that 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. 1033, 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. 42), however, EP 005 is concerned with the vascular effects of elevated homocysteine levels, such as myocardial and cerebral infarction. Ex. 1033, 2:4–6. In addition, as also noted by Patent Owner (PO Resp. 42–43), EP 005 does not teach treatment of any cancer patients. Moreover, EP 005 does not discuss antifolates generally, but only once lists methotrexate as a drug that may increase homocysteine levels, and mentions leukemia and "other cancers" as causes of elevated homocysteine levels. As Patent Owner contends (PO Resp. 43), Niyikiza II—in contrast to EP 005—reported that pemetrexed did not increase homocysteine levels, and was not correlated with MMA levels. Thus, we agree with Patent Owner, and find that Niyikiza does not provide a reason to lower homocysteine levels *per se* with both folic acid and vitamin B12, and EP 005 does not provide a reason to administer its formulation in combination with a drug, that is pemetrexed, that has not been shown to

induce abnormally elevated homocysteine levels. *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 medical condition was only mentioned once, and that there was no data supporting a causation theory).

That is, as noted by Patent Owner (PO Resp. 38–39), the baseline homocysteine levels reported by Niyikiza that correlated with increased toxicities with pemetrexed treatment, were not, by themselves, abnormally high, so would not warrant treatment *per se*. According to Patent Owner (PO Resp. 38), Niyikiza teaches that homocysteine levels did not appear to change from baseline during treatment with pemetrexed. Petitioner's expert, Dr. Schiff, appears to agree that the ordinary artisan would not have thought that the baseline homocysteine levels taught by Niyikiza to be abnormally high. Specifically, Dr. Schiff testifies:

> 19 Q. Okay. Would the person of ordinary
> 20 skill in 1999 have thought a homocysteine level of
> 21 10 was outside the normal range?
> 22 A. No.
> 23 Q. Where would they have thought the upper
> 24 limit of the normal range was?
> 25 A. They would have defined it based on the
> 2 upper limit of normal in the laboratory they used
> 3 for their own patients. And that is, as I said,
> 4 quite variable.
> 5 Q. Okay. But you are comfortable saying
> 6 that they would not have viewed a level of 10 as
> 7 abnormally high.
> 8 A. Exactly.

Ex. 2026, 121:19–122:8.

Thus, given that EP 005 defines elevated homocysteine levels as greater that 16.3 µM, and Niyikiza's teaches that homocysteine levels of

greater than or equal to 10 µM correlated with elevated toxicities, we find that EP 005 would not have provided a reason to pretreat with vitamin B12 as well as folate before administration of pemetrexed. And to the extent that high homocysteine levels were of concern, as we found above, the prior art provided a reason to pretreat with folic acid, but did not provide a reason to pretreat also with vitamin B12. Thus, we agree with Patent Owner (PO Resp. 43) that EP 005 does not provide information as to how pretreatment with folic acid and vitamin B12 would impact the effects of methotrexate on cancer, or any associated toxicities.

Petitioner further relies on Calvert as showing that low amounts of either vitamin B12 or folate will result in elevated homocysteine. Reply 10 (citing Ex. 1074, 150:12–16, 161:1–164:3). Petitioner argues that based on this teaching, the ordinary artisan would have added vitamin B12 to the known folic acid pretreatment regimen of Worzalla and Hammond I. *Id.* at 44. Counsel for Petitioner acknowledged that our reviewing court found Calvert to "merely note in passing that vitamin B12 can be related to homocysteine levels and folate biochemical pathways." Tr. 147:13–19[28] (quoting *Eli Lilly*, 845 F.3d at 1375). Our reviewing court further found no testimony to support the contention that Calvert "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 testimony to support its

[28] 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.

contention that the ordinary artisan would have been motivated to use vitamin B12 as a pretreatment for pemetrexed. Tr. 147:22–148:1. Petitioner, however, does not specifically explain how that testimony 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 supplementation prior to receiving any antifolate, with or without folic acid." *Eli Lilly*, 845 F.3d at 1373–74 (internal quotation marks omitted); Tr. 147:16–148:1.

In addition, we do not find persuasive Petitioner's argument (Pet. 30–31; Reply 19–20) that the ordinary artisan would have also pretreated with vitamin B12 as well as folic acid to avoid masking an unknown vitamin B12 deficiency. Petitioner has not explained why the ordinary artisan would have added vitamin B12 when MMA levels are not correlated with pemetrexed toxicity. Nor has Petitioner explained why, if it was so well known that treatment with folic acid may mask a vitamin B12 deficiency that could lead to irreversible neuropathy, the prior art references of record in this proceeding, such as Hammond and Worzalla, that did teach pretreatment with folic acid, did not also pretreat with vitamin B12.

As to Petitioner's argument (Reply 13) that Patent Owner explained to the FDA "that the 'B12 deficiency marker, methylmalonic acid, was highly correlated with homocysteine and was therefore removed from the initial multivariate analysis conducted in 1998 to eliminate issues of collinearity'" (Ex. 1088, 3), we note that Petitioner does not assert, nor does it establish, that Exhibit 1088 is prior art to challenged claim 1. Furthermore, in *KSR*, the Supreme Court reaffirmed that, despite the importance of a flexible and

commonsense 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 statement made by Patent Owner in its letters to the FDA were made in after the invention of the Lilly scientists and researchers. 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 administering pemetrexed to treat cancer.

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.

As to the claim requirement of pretreating with vitamin B12, Patent Owner additionally cites ViDAL[29] as "expressly counsel[ing] patients with cancer against taking vitamin B_{12}, stating that 'due to the action of vitamin B_{12} on the growth of tissues with a high rate of cellular multiplication, the risk of exacerbation must be taken into account.'" PO Resp. 36 (citing Ex. 2032, 24, 26, 28–29; Ex. 2059, 3, 6; Ex. 2120 ¶ 89; Ex. 2060, 48). Patent Owner argues further that both Arsenyan and Sofyina recognize the ability of vitamin B12 to stimulate tumor growth, and that Arsenyan reported that when mice were pretreated with methylcobalamin (a metabolite of vitamin B12) there was a total loss of activity of methotrexate. *Id.* (citing Ex. 1023, 1300; Ex. 1026, 1, 3; Ex. 2041, 1, 3; Ex. 2058, 4017; Ex. 2120 ¶¶ 88–90).

ViDAL, Petitioner asserts, does not support Patent Owner's argument that the ordinary artisan would not pretreat with vitamin B12, and neither do Arsenyan and Sofyina. Reply 21. Specifically, Petitioner argues that "*ViDAL* states only that the possibility of tumor growth 'must be taken into account' generally; it contains no mention of pemetrexed, no references, and no supporting data – indicia Dr. Chabner testified are important in assessing reliability." *Id.* (citing Ex. 109:15–18, 267:6–13). Furthermore, Petitioner asserts, the *Physician's Desk Reference* lacks a similar entry and affirmatively recommends vitamins in conjunction with chemotherapy. *Id.* (citing Ex. 1074, 106:17–107:4, 108:2–6; Ex. 1092; Ex. 1106; Ex. 1086, 51:3–57:2; Ex. 1075 ¶¶ 93–94).

[29] VIDAL LE DICTIONNAIRE (74th ed. 1998) (translation) (Ex. 2032) ("ViDAL"). The page numbers cited refer to the page number added by Patent Owner.

As to Arsenyan and Sofyina, Petitioner contends that "Arsenyan shows mice that received both methotrexate and methylcobalamin, a form of vitamin B_{12}, experienced an overall ***increase*** in survival from 0 days (methylcobalamin alone) to 21 days (methylcobalamin + methotrexate)." *Id.* (citing Ex. 1023, 1300; Ex. 1075 ¶ 89). In addition, Petitioner asserts, "[o]n its face, Sofyina states that the 'most effective inhibition of tumour growth and the longer survival of the animals was achieved in combined application of methylcobalamine with methotrexate.'" *Id.* (citing Ex. 1026, 7; Ex. 1074, 321:2–15; Ex. 1075 ¶¶ 90–91).

We recognize that ViDAL does note in regard to vitamin B12 preparations that "due to the action of vitamin B_{12} on the growth of tissues with a high rate of cellular multiplication, the risk of exacerbation must be taken into account." Ex. 2032, 24. However, we take that as an acknowledgement of the effect of folate metabolism on DNA synthesis. That is, as both Patent Owner and Petitioner agree (*see* Section III.ii.b, above), folate dependent enzymes are involved in the synthesis of DNA precursors. The enzyme that is required to convert folate to an active form that can be used to make DNA precursors requires vitamin B12. Antifolates, therefore, act by interfering with DNA synthesis. Thus, vitamin B12 may act to increase the amount of active folate available for the synthesis of DNA precursors. Thus, we find that the statement in ViDAL neither helps nor hurts Patent Owner, but do find it is one of the many factors that the ordinary artisan would take into account in determining whether to pretreat with vitamin B12.

Arsenyan looks at the influence of methylcobalamin, that is, a form of vitamin B12, on the antineoplastic activity of methotrexate. Ex. 1023, 1299.

Arsenyan used mice in which tumors had been implanted. *Id.* at 1301. Table 2 of Arsenyan is reproduced below:

TABLE 2. Results of Combined Action of Methylcobalamin and Methotrexate on the Growth of Ca-755 (BDF_1)

Preparations	Dose of preparation	Inhibition of tumor growth* after course of administration of preparations, % of control		Increase in lifetime of animals, %
		1st-2nd day†	7-8th day†	
Methotrexate	10 mg/kg	94	51	19‡
Methylcobalamin	10 μg/kg	+180	+65	0
Methylcobalamin + methotrexate	10 mg/kg (simultaneously) 10 μg/kg	94	76	60
Methylcobalamin + methotrexate	10 μg/kg (methotrexate was administrated 6 h after methylcobalamin)	+36	+62	21‡

*Average results of five series of experiments.
†Period after transplantation of tumor.
‡$P > 0.05$; in all remaining cases $P < 0.05$. In the case of combined influence, the results obtained were evaluated relative to methotrexate.

Id. at 1300.

As can be seen in Table 2, administration of methylcobalamin alone increased tumor growth, and there was no increase in the lifetime of the animals. Simultaneous administration of methylcobalamin and methotrexate had the largest increase in the lifetime of the animals. When methotrexate was administered 6 hours after administration of methylcobalamin (that is, after pretreatment with vitamin B12), there was no statistical difference in the lifetime of the animals from the administration of methotrexate alone. According to Arsenyan, the "interval between administration of methylcobalamin and methotrexate is of vital importance," and "when methylcobalamin was preliminarily administered (6 h before the use of methotrexate), a total loss of activity of methotrexate was observed." *Id.* at 1302.

Dr. Schiff, Petitioner's expert, however, explains:

> the legend makes clear that the ‡ symbol indicates a lack of statistical significance "relative to methotrexate." (Ex. 1023, Arsenyan at 1300.) . . . . [T]he 21% increase in survival for mice receiving methylcobalamin pretreatment and methotrexate was not statistically significant relative to methotrexate alone. In other words, Arsenyan shows that methylcobalamin pretreatment did not significantly improve mice's survival over those receiving methotrexate alone, but that the methylcobalamin pretreatment had no detrimental impact on methotrexate's efficacy. A 21% increase in lifespan versus the control group would certainly be significant.

Ex. 1075 ¶ 90.

Thus, even if we were to discount Arsenyan's statement that "when methylcobalamin was preliminarily administered (6 h before the use of methotrexate), a total loss of activity of methotrexate was observed," even under Dr. Schiff's interpretation, there is no significant improvement in the activity of the methotrexate with vitamin B12 pretreatment. Ex. 1023, 1302. At best, Arsenyan would suggest simultaneous administration of methotrexate and vitamin B12.

Sofyina looked at the antitumor effects of antagonists of the cobalamin coenzyme and methotrexate. Ex. 1026, 2–3. Sofyina also used mice in which tumor cells were implanted. *Id.* at 4. According to Sofyina, they "established the antitumor activity of the antagonists of cobalamine coenzyme." *Id.* at 7. We find those teachings of Sofyina to add very little to the teachings of ViDAL and Arsenyan.

Finally, we find that ViDAL, Arsenyan, and Sofyina are of little relevance to whether the ordinary artisan would pretreat a cancer patient with vitamin B12 before administering pemetrexed. As Petitioner's expert, Dr. Schiff declares, none of Arsenyan, Sofyina, or ViDAL "concerns

pemetrexed," and an ordinary artisan would consider pemetrexed-specific teachings, such as those of Niyikiza, to be more relevant. Ex. 1075 ¶ 89. As discussed above, as Niyikiza teaches that MMA levels do not correlate with pemetrexed toxicity, and as increased MMA levels correlate with vitamin B12 deficiency, we find that ViDAL, Arsenyan, and Sofyina do not affect our finding 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.

Patent Owner contends further that the additional references cited by Petitioner do not support pretreating with vitamin B12 before administration of pemetrexed. PO Resp. 46–48. As to Carrasco, Patent Owner argues that reference is not prior art. *Id*. at 46 n.5. Carrasco, Patent Owner argues, describes giving vitamin B12 and folic acid during methotrexate chemotherapy. Thus, Carrasco does not teach pretreating with vitamin B12 and folic acid, but rather, teaches giving the patient vitamin B12 and folic acid after receiving methotrexate to treat megablastic anemia, a symptomatic vitamin deficiency. *Id*. at 46. 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.* at 47 (citing Ex. 1032; Ex. 2120 ¶ 182). Thus, all that can be taken from the teachings of Carrasco, Patent Owner asserts, is that if a patient is diagnosed with a vitamin deficiency, the ordinary artisan would first treat the cancer and then the deficiency, and, thus, Carrasco provides insufficient reason to add vitamin B12 pretreatment. *Id.* (citing Ex. 2120 ¶¶ 182–186).

According to Petitioner, however, Carrasco confirms that the ordinary artisan would not have any concerns about pretreating with vitamin B12, as

it "reports a patient treated with both folic acid and vitamin B_{12} ***during*** a methotrexate treatment regimen." Reply 20 (citing Ex. 1032). Petitioner asserts further that Patent Owner's expert, Dr. Chabner, acknowledged that "Carrasco evidences an oncologist having no concern about these vitamins' impact on an antifolate's efficacy." *Id.* (citing Ex. 1074, 189:25–190:14; Ex. 1075 ¶ 102).

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. 1032, 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 767–768. Thus, the folic acid and vitamin B12 were administered after the methotrexate 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 to ameliorate the toxicity of pemetrexed.

Patent Owner notes that Petitioner relies on Mendelsohn as suggesting "'that adequate levels of vitamin B_{12} may have a significant effect on toxicity' of antifolates." PO Resp. 47 (quoting Pet. 33) (citing Ex. 1012). Mendelsohn, Patent Owner argues, dealt with the "antifolates lometrexol and LY309887, hypothesiz[ing] that because the 'biochemical pathways that

utilize folate cofactors also require adequate amounts of vitamin B_{12} and B_6,' the status of folic acid, vitamin B_{12}, and vitamin B_6 in a patient 'may [significantly] influence the severity of toxicity observed during chemotherapy.'" *Id.* (quoting Ex. 1012, 270). Niyikiza, however, dealt with pemetrexed, the antifolate required by challenged claim 1, and, therefore, Patent Owner maintains, the ordinary artisan would view Mendelsohn in light of Niyikiza's teaching of a lack of correlation between MMA and pemetrexed toxicity, and determine that Mendelsohn's hypothesis does not apply to the antifolate pemetrexed. *Id.* at 47–48. In addition, Patent Owner argues, Mendelsohn does not suggest any course of action, does not suggest pretreatment with vitamin B12, and provides no evidence to support its hypothesis. *Id.* at 48 (citing Ex. 2026, 47, 158–159).

As to Ubbink I (Ex. 1039), Brattström (Ex. 1020), Brönstrup (Ex. 1040), and Ubbink II (Ex. 1041), Patent Owner contends that those references are from the "nutritional literature," and none of the references teach or suggest pretreating a cancer patient with vitamin B12 before administering an antifolate such as pemetrexed. PO Resp. 48. Rather, according to Patent Owner, they discuss homocysteine levels in the nutritional and cardiovascular context. *Id.* (citing Ex. 2120 ¶¶ 119–120). Patent Owner asserts "[t]hey provide no information concerning the management of antifolate-induced toxicities, let alone what effects a combination of folic acid and vitamin B_{12} pretreatment would have on a cancer patient receiving an antifolate," arguing that those "references are thus irrelevant." *Id.*

Petitioner responds that Patent Owner is contradicting itself by dismissing these references, as well as EP 005, as irrelevant, given that

Patent Owner relies "on general nutritional concepts relating to the methyl trap not tied to cancer." Reply 14. In addition, Petitioner asserts, Patent Owner "relied on some of these same 'nutritional' references before the FDA when seeking approval to pretreat cancer patients with vitamins before administering pemetrexed." *Id.* (citing Ex. 1076,[30] 20). Finally, Petitioner argues that the '209 patent refers to nutritional references when discussing the background of the invention, and the ordinary artisan would have been aware of such references. *Id.* at 14–15 (citing Ex. 1001, 2:16–24; Ex. 1004 ¶ 13).

Again, although we find that these references are background to the claimed invention, they are not as relevant as references dealing specifically with the administration of pemetrexed to cancer patients, such as Niyikiza. And again, the references do not affect our finding 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.

Moreover, we note as to Mendelsohn, that although Mendelsohn teaches that the "biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B_{12} and B_6," when it explored the possibility of addressing toxicities associated with antifolate administration using dietary supplementation, it only looked at pretreating with folic acid. Ex. 1012, 270, 272. Thus, it does not provide any additional support than the references relied upon Petitioner in its challenge to claim 1, which

[30] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co. to Alvis Dunson, Project Manager, Food & Drug Admin. (Feb. 16, 2000) (Ex. 1076).

requires pretreating with vitamin B12 as well as folic acid when administering pemetrexed.

Petitioner argues that Patent Owner's characterization of the Hammond Abstracts, Worzalla, and Laohavinij, are contradicted by its correspondence with the FDA near or prior to June 30, 2000, which is the earliest priority date of the '209 patent. Reply 8. In particular, Petitioner contends that in February of 2000, Lilly told the FDA that Worzalla supported pretreatment with folic acid and vitamin B12, telling the FDA that Worzalla demonstrated that it was possible to decrease toxicity, while still retaining efficacy. *Id.* at 8–9 (citing Ex. 1084,[31] 5). As for the Hammond Abstracts, Petitioner asserts that Patent Owner told the FDA that they suggested that folic acid supplementation allowed for dose escalation. *Id*. at 9 (citing Ex. 1077,[32] 8, 19). In addition, Petitioner argues, Patent Owner relied on Laohavinij to support adding vitamin pretreatment to the protocol. *Id*. (citing Ex. 1077, 3, 7–8, 24).

Petitioner contends:

> Lilly also told FDA that it was known in 1999 that folic acid supplementation with pemetrexed would be beneficial, noting that it opted to "proceed with vitamin supplementation (folic acid together with vitamin B12)" because "external consultants were in unanimous agreement that the addition of folic acid should lower plasma homocysteine levels and thus offer protection to patients." Yet, Lilly now claims that the very same prior art it relied on to seek FDA approval taught just the opposite.

[31] Briefing Document (Feb. 16, 2000) (Ex. 1084).

[32] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Food & Drug. Admin. (Dec.3, 1999) (Ex. 1077). The page numbers refer to page numbers added by Petitioner.

Id. (citation omitted) (quoting Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Project Manager, Food & Drug Admin. 7–8[33] (Jan. 25, 2000) (Ex. 1085)).

As noted above, we decline to read the references in view of Patent Owner's correspondence with the FDA, which Petitioner has not asserted or demonstrated are prior art. As stated above, the prior art referenced by Lilly in its correspondence 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 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

[33] The page numbers refer to page numbers added by Petitioner.

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, skepticism, copying, 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. 57 (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.* (citing Ex. 2116, 750–758, 760–765, 771–775). In addition, 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 58 (citing Ex. 2091, 3; Ex. 2120 ¶¶ 33h, 225–227).

According to Patent Owner, in an ongoing Phase III trial, "an alarming 7% of patients died, apparently due to severe pemetrexed toxicities," threatening to halt development of the drug. *Id.* at 11 (citing

Ex.2103, [34] 2; Ex. 2107, 16). 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 11, 58 (citing Ex. 2100,[35] 8044, 8046; Ex. 2103; Ex. 2104,[36] 1; Ex. 2105[37]; Ex. 2106[38]; Ex. 2109,[39] 10; Ex. 2108,[40] 2; Ex. 2116, 787–788, 821–822, 845).

As to praise by others, Patent Owner argues that the invention was praised by others after its implementation. *Id.* at 59. 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. *Id.* (citing Ex. 2116, 845).

Petitioner responds that Patent Owner's "purported skepticism is both legally and factually flawed." Reply 25. Specifically, Petitioner asserts that

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

[35] LY231514 (MTA) End of Phase 2 Meeting with the FDA Clinical Issues (Sept. 25, 1998) (Ex. 2100).

[36] Fax from Alvin Dunson, Project Manager, Dep't of Health & Human Servs., to John Worzalla, Eli Lilly & Co. (Dec. 21, 1999) (Ex. 2104).

[37] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Food & Drug Admin. (Dec. 22, 1999) (Ex. 2105).

[38] Fax from Alvis Dunson, Project Manager, Dep't of Health & Human Servs., to John Worzalla, Eli Lilly & Co. (Jan. 6, 2000) (Ex. 2106).

[39] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Food & Drug Admin. (Mar. 20, 2000) (Ex. 2109).

[40] Meeting Minutes (Mar. 1, 2000) (Ex. 2108).

Dr. Niyikiza's testimony at the district court is hearsay, and in some cases, double hearsay, and Petitioner has not had a chance to cross-examine him about that testimony.[41] *Id.* at 25–26.

Petitioner contends further that Patent Owner misinterprets the statements of the FDA made during the pemetrexed approval process. *Id.* at 26. In particular, Petitioner relies on the Declaration of Dr. Ross, a former FDA Deputy Director, who testifies that the FDA's concerns were about the ability to still obtain statistically meaningful results after the change in protocol, which is why the change was "at Lilly's risk." *Id.* (citing Ex. 1093 ¶¶ 13–28).

As to Dr. Chabner's statements made in the *Wall Street Journal*, Petitioner asserts that Dr. Chabner admitted he was not aware of the '974 patent or EP 005, and, thus, he based his statements on his own experience with methotrexate and not as one of ordinary skill in the art. *Id.* at 26–27 (citing Ex. 1074, 182:15–183:4, 282:8–15, 300:7–20).

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 determine that it is not evidence of skepticism, as it pertains only to pretreatment with folic acid, and not pretreatment with both vitamin B12 and

[41] 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. Given that we are at the final written decision, we *deny* Petitioner's motion as moot. We note that we placed no reliance on Dr. Niyikiza's testimony from the district court trial, and, therefore, determine that there has been no prejudice to Petitioner.

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, however, 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 preponderance of the evidence of record support a finding of skepticism of others, and particularly, the FDA. 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. PO Resp. 11 (citing Ex. 2017,[42] 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." Ex. 2017, 16 (*see* PO Resp. 11) According to Lilly, enrolling patients in trials without vitamin supplementation "would

[42] Letter from Gregory T. Brophy, Dir., Eli Lilly & Co., to Alvis Dunson, Project Manager, Food & Drug Admin. (Feb. 16, 2000) (Ex. 2017). The page numbers refer to the page numbers added by Patent Owner.

be ill-advised," 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 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.* One of the FDA's concerns in that regard was having a well-controlled trial. Ex. 2108, 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 and 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.

We do not disagree with Petitioner (Reply 26), however, that part of the FDA's concern about Lilly changing its Phase III clinical trial was obtaining statistically relevant evidence. 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 other 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, Patent Owner has not established that is by an "other," rather, the statement was made by 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 sufficiently demonstrated that 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 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 nonobviousness. Thus, weighing all of the evidence of obviousness of record, we conclude that Petitioner has failed to demonstrate that independent challenged claims 1 and 12 of the '209 patent are rendered obvious by the combination of Calvert, Niyikiza I, Worzalla or Hammond I, EP 005, and the '974 patent. As all the challenged 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 Calvert, Niyikiza I, Worzalla or Hammond I, EP 005, and the '974 patent by a preponderance of the evidence of record.

D. Petitioner's Motion to Exclude

Petitioner seeks to exclude Patent Owner's Exhibit 2116, as well as paragraphs 24–28 and 44–78 of Exhibit 2118. Mot. Exclude 1.

Exhibit 2116 is the trial testimony of Dr. Niyikiza in a district court proceeding in which Petitioner Sandoz was not a party. *Id*. Petitioner argues that the testimony should be excluded as hearsay, improper expert testimony, and an improper attempt to circumvent cross-examination. *Id.* In addition, Petitioner asserts that Exhibit 2116 is not a complete exhibit, as it omits the cross-examination and re-direct of Dr. Niyikiza. *Id.* at 11.

As noted by Patent Owner, however, Petitioner put the district court's findings of fact, as well as excerpts of Dr. Niyikiza's testimony, into evidence. Opp. Mot. Exclude 1–2 (citing Ex. 1003; Ex. 1036). Patent Owner notes further that it also filed the 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 and excerpts of Dr. Niyikiza's testimony filed by Petitioner, and, thus, we *deny* Petitioner's Motion to Exclude as to Exhibit 2116.

Exhibit 2118 is the Declaration of Dr. Steven H. Ziesel. Mot. Exclude 11. According to Petitioner, "[p]aragraphs 24-28 and 44-78 of Dr. Zeisel's declaration (Exhibit 2118) should be excluded because they pertain to topics within the expertise of an oncologist for which Dr. Zeisel is not qualified to testify under Fed. R. Evid. 702." *Id.* at 12. Petitioner's objection, however,

goes more to the weight of the testimony, rather than its admissibility. We, therefore, also *deny* Petitioner's Motion to Exclude as to Exhibit 2118.

III. CONCLUSION

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