

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

Case IPR2024-00623
Patent 11,325,974 B2

PATENT OWNER'S SUR-REPLY

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LIST OF EXHIBITS

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2001	RESERVED
2002	Curriculum Vitae of Dr. Nils Lonberg
2003	Dung T. Le, Sidney Kimmel Comprehensive Cancer Center, PD-1 Blockade in Tumors with Mismatch Repair Deficiency, Presentation at 2015 ASCO Annual Meeting (May 30, 2015) (abstract available at https://meetings.asco.org/abstracts-presentations/109904)
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2007	News Release, Merck, Merck Receives Accelerated Approval of KEYTRUDA® (Pembrolizumab), the First FDA-Approved Anti-PD-1 Therapy (Sept. 4, 2014) available at https://www.merck.com/news/merck-receives-accelerated-approval-of-keytruda-pembrolizumab-the-first-fda-approved-anti-pd-1-therapy/

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2038	Briukhovetska et al., <i>Interleukins in Cancer: From Biology to Therapy</i> , 21 Nature Reviews Cancer 481-99 (June 3, 2021)
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2069	Exhibit 14 to Johns Hopkins University Corrected Answer and Counterclaims to Complaint, Merck Sharp & Dohme LLC v. The Johns Hopkins University, Case No. 1-22-cv-03059-JRR, D.I. 17-14 (D. Md. April 21, 2023)

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2072	Declaration of Dr. Nils Lonberg
2073	Connolly et al., <i>Novel Mouse Models for Cancer Immunology</i> , Annual Review of Cancer Biology 6:269-91 (2022)
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2119	Ethical Guidelines, Ethics in Clinical Research, NIH Clinical Center, https://www.cc.nih.gov/recruit/ethics (last accessed Sept. 26, 2024)
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2121	The Cancer Letter, Vol. 43, No. 38, Oct. 13, 2017
2122	The Cancer Letter, Vol. 48, No. 23, June 10, 2022
2123	<i>How Beth Carner went from six weeks left to live with stage 4 colon cancer to complete remission</i> , Cancer History Project (June 10, 2022), https://cancerhistoryproject.com/article/how-beth-carner-went-from-six-weeks-left-to-live-with-stage-4-colon-cancer-to-complete-remission/
2124	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (May 23, 2017)

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2125	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Oct. 2015)
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2131	Investigator Initiated Clinical Trial Research Agreement between The Johns Hopkins University and Merck Sharp & Dohme Corp., dated August 14, 2013
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2150	21 U.S.C. § 331 - Prohibited acts
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2167	Highly Confidential Attorney Eyes Only Document 1 – Protective Order Material
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2169	Highly Confidential Attorney Eyes Only Document 4 – Protective Order Material
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2171	Highly Confidential Attorney Eyes Only Document 6 – Protective Order Material
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2193	Merck & Co., Inc. 2014 SEC Form 10-K, dated February 27, 2015
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2195	Merck Sharp & Dohme LLC Private Company Profile at S&P Capital IQ

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2196	Johns Hopkins University Educational Institution Profile at S&P Capital IQ
2197	Research & Faculty, Johns Hopkins University, https://www.jhu.edu/research/ (last accessed Oct. 3, 2024)
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2243	Bristol-Myers Squibb 2020 SEC Form 10-K (Excerpt)
2244	Bristol-Myers Squibb 2021 SEC Form 10-K (Excerpt)
2245	Bristol-Myers Squibb 2022 SEC Form 10-K (Excerpt)
2246	Bristol-Myers Squibb 2023 SEC Form 10-K (Excerpt)
2247	Merck SEC Form 10-Q, for quarterly period ended March 31, 2018 (Excerpt)
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2287	Support & Resources JEMPERLI (dostarlimab-gxly), available at https://jemperli.com/endometrial-cancer/support-resources/
2288	GSK 2021 Annual Report
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2402	Copy of EX1005, ClinicalTrials.gov, NCT01876511, “Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C),” (June 10, 2013), marked at January 6 th Deposition of Dr. Neugut
2403	Board Email regarding Motion to Seal dated October 4, 2024
2404	Confidential_Deposition Transcript of Paul E. Oberstein, M.D., February 19, 2025
2405-2410	RESERVED
2411	Confidential_Deposition Transcript of Sean D. Sheridan, Ph.D., February 14, 2025
2412-2499	RESERVED
2500	Declaration of Frank E. Scherkenbach in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2501	Declaration of Corrin N. Drakulich in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney

Exhibit Number	Description
2502	Declaration of Christina D. Brown-Marshall in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2503	Declaration of Casey M. Kraning in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2504	Declaration of Madelyn S. McCormick in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2505	Declaration of Sarah E. Jack in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney

I. INTRODUCTION

Recognizing that its Petition necessarily fails based on the absence of key disclosures in the MSR, Merck engaged a new, Merck-sponsored declarant (EX2404, 229:21-24), Dr. Paul Oberstein, to offer opinions on Reply. But no amount of expert opinion or attorney argument can cure the MSR's deficiencies. In the end, JHU's arguments stand unrebutted: (1) the MSR does not expressly or inherently disclose multiple limitations related to prior therapy and metastatic cancer; (2) the MSR is an "invitation to investigate" that does not expressly or inherently disclose any clinical results; (3) the MSR meets the Experimental Use factors; and (4) objective indicia refute obviousness.

Rather than rebutting JHU's arguments, Merck presents the Board with mischaracterizations of deposition testimony and allegations of contradictory statements to FDA and the Patent Office. Most glaringly, Merck rewrites the claims and the MSR, reducing each to two generic steps that strip out critical claim limitations and other information to create a false equivalency. Reply, 1, 22-24. The Board should uphold patentability of the claims.

II. ALL GROUNDS FAIL BECAUSE THE MSR DOES NOT ANTICIPATE OR RENDER OBVIOUS THE CHALLENGED CLAIMS

A. Merck's Inherency Arguments Fail on Multiple Levels

It is undisputed that the MSR does not explicitly disclose the limitations requiring “prior cancer therapy drug,” “progressed after...the prior cancer therapy drug,” “metastatic” cancer, or the claimed clinical outcomes. POR, 6-15, 24-31; Reply, 10-17. Therefore, Merck must resort to inherency to fill those holes.

1. The MSR Does Not Inherently Disclose the Claimed Clinical Outcomes

In *In re Montgomery*, the Federal Circuit found that a clinical trial protocol may inherently anticipate a method claim if the results “inevitably flow” from the prior art disclosure. However, in *Montgomery*, the prior art trial disclosure “in all relevant respects” was “identical to the patent itself.” 677 F.3d 1375, 1383 (Fed. Cir. 2012). Here, the MSR disclosure is not remotely the same as the patent—as JHU explained (POR, 11), the patent specification includes and relies critically on data **resulting** from the MSR. The prior art MSR disclosure is not “[i]n all relevant respects...identical to the patent itself,” as it was in *Montgomery*. And even if it were, the MSR does not disclose several claim limitations. Merck highlights these differences by omission when it argues that the MSR disclosed a generic two-step method divorced from the actual claimed methods. Reply, 1-2. Because the

claimed method is different from the method disclosed by the MSR, the results claimed by the '974 Patent cannot “inevitably flow” from the MSR.

Montgomery also distinguishes clinical trials that are at “an advanced stage of testing designed to secure regulatory approval,” which can inherently disclose a method of treatment, from what we have here, i.e., “an invitation to investigate, [which] is not an inherent disclosure.” *Id.*, 1382 (citation omitted). Contrary to Merck’s assertions (Reply, 10-11), the majority opinion in *Montgomery* explicitly ***agreed*** with the dissent on this point. *Id.* (“To be sure, ***as the dissent points out***, ‘[a]n invitation to investigate is not an inherent disclosure.’”).¹

JHU previously explained why the MSR was an “invitation to investigate.” (POR, 11-15). [REDACTED]

[REDACTED] That the IND included a scientific rationale—as Merck argues—does not negate that the MSR was an invitation to investigate, because ***all*** clinical trials have a rationale. EX2404, 155:3-156:12; Reply, 10-12. The language of JHU’s scientific rationale demonstrates the investigative nature of their proposed clinical trial:

[REDACTED]
[REDACTED]
[REDACTED]

¹ All emphasis added herein unless otherwise noted.

[REDACTED]

EX1116, 18; *see also id.*, 19 (“[REDACTED]” 40

(“[REDACTED]”

Contrary to Merck’s suggestion, no Federal Circuit authority requires a patent owner to include a specific phrase (“abstract theory”) in its study proposal to describe its hypothesis or for the FDA to question the investigator’s scientific rationale before a proposed study qualifies as an “invitation to investigate.” Reply, 10-11.

JHU’s arguments here are consistent with what it told FDA in the IND. Reply, 10-11. The JHU inventors formed a hypothesis based on an anomalous result seen in a single patient in an otherwise unsuccessful study (32 other patients did not respond) of a different drug and different hypothesis. *Compare* POR, 45 (“the JHU inventors hypothesized that the response may have been tied to the patient’s MSI-H status”), *with* EX1116, 39-40 [REDACTED]

[REDACTED]

[REDACTED]; *see also* EX1245, 80:17-85:7 (Dr. Lonberg testifying “[T]hat is not an anticipated outcome. That is a hypothesis.”).

The investigative nature of the MSR is further buttressed by JHU's showing that the MSR was the first in a long series of proposal updates leading to the invention becoming ready for patenting (POR, 18-24). Against this backdrop, Merck's interpretation of inherency, which would require JHU to file its patent application before even posting the MSR clinical trial announcement, makes no sense, particularly where "those skilled in this art would not accept anything short of such human clinical trials." *Ex Parte Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (B.P.A.I. 1991); POR, 15-16.

2. The MSR Does Not Inherently Disclose "a Prior Cancer Therapy Drug" or "Progressed After...the Prior Cancer Therapy Drug"

The standards for inherent anticipation are both clear and strict. To fill a gap based on inherency, the missing disclosure must be "necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Merck's inherency arguments defy this mandate. In short, Merck posits that a study conducted in furtherance of the MSR *might have* included patients who had received a prior cancer therapy drug or who progressed after receiving the prior drug. Such speculation does not suffice for inherent anticipation. In *MEHL/Biophile Int'l. Corp. v. Milgraum*, the Federal Circuit explained that the possibility a reference *might disclose* a claim limitation "does not legally suffice to show anticipation" because "[o]ccasional results are not

inherent.” 192 F.3d 1362, 1365 (Fed. Cir. 1999). That the MSR discloses treating cancer patients *that could* be within the claimed subset cannot inherently anticipate results later obtained by treating *only* patients within the claimed subset.

Not only does Merck disregard the applicable law, it disregards unhelpful facts. For example, Merck’s Dr. Oberstein conceded that a patient *could be* included in the clinical trial proposed by the MSR even if she had not received a prior cancer therapy drug. EX2404, 276:7-25; *see also id.*, 277:2-10; EX2163, 99:13-21 (Dr. Neugut agreeing MSR “leaves out” previous treatment and progression). JHU’s Dr. Lonberg agreed, testifying the MSR “does not require treatment of only patients who have received at least one prior cancer therapy.” EX1245, 57:10-14. Dr. Lonberg testified the MSR provides “no general exclusion for prior therapies,” paralleling Drs. Oberstein and Neugut’s testimony. *Id.*, 56:18-57:4; EX2404, 277:2-10; EX2163, 99:13-21. Because the claimed requirement that the patient receive a prior cancer therapy drug is *not necessarily present* in the MSR, the MSR cannot inherently anticipate this limitation.

3. The MSR Does Not Inherently Disclose Treating “Metastatic” Cancer

Merck’s inherency challenge to dependent claims 5-6, which require the cancer to be “metastatic,” fails for similar reasons. Metastatic cancer is neither expressly nor inherently disclosed by the MSR. Inclusion criteria 1-4 (EX1005, 5)

identify the types of cancers the patients in the proposed trial must have; none *require* metastatic cancer.

Merck tries to import the word “metastatic” into the MSR by asking the Board to disregard Dr. Neugut’s deposition testimony disavowing any equivalence between the disclosed “measurable disease” and the claimed “metastatic” cancers. EX2163, 14:3-12, 14:13-15:12 (explaining the difference). But Merck provides no reason to do so.

Merck also points to Dr. Lonberg’s testimony that the MSR does not *exclude* patients with metastatic disease. EX1245, 58:3-10; *see also id.*, 49:14-51:7. Whether such patients were excluded from the proposed study is a far cry from evidence of the MSR being *limited to* or necessarily including metastatic cancer patients as claimed. If the MSR was so limited, the inclusion criteria would reflect this, but they do not. *See*, EX2404, 274:16-275:18. Once again, Merck relies upon the “mights” and “maybes” which are insufficient to support an inherent anticipation claim. “Inherency...may not be established by probabilities or possibilities.” *Montgomery*, 677 F.3d at 1380.

B. Merck Fails to Rebut Experimental-Use Negation

It is undisputed that JHU was required to post the MSR to ClinicalTrials.gov before beginning the clinical trial that yielded data supporting the ’974 Patent’s claims. JHU also provided un rebutted evidence demonstrating applicability of the

experimental-use exception. POR, 18-24. Merck does not respond to that analysis. It does not dispute, for example, that the MSR was required by law, necessary to establish the usefulness of the claimed methods, and done for no commercial purpose. *Id.* The MSR is thus precisely the type of activity that courts have found support experimental-use negation. *See Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998).

Merck instead declares—without analysis or elaboration—that “the Federal Circuit has found that ClinicalTrials.gov study records, like the MSR, are Section 102 prior art.” Reply, 8 (citing *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024)). That is true but irrelevant—the *Salix* panel never addressed whether a ClinicalTrials.gov posting is subject to experimental negation. Because the panel was not presented with this issue, the panel cannot have resolved it. *Cooper Indus., Inc. v. Aviall Servs., Inc.*, 543 U.S. 157, 170 (2004).² Thus, JHU’s experimental-use argument is not contrary to any Federal Circuit precedent.

² The same is true for *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, IPR2022-00578, Paper 78 at 24-28 (P.T.A.B. Aug. 29, 2023).

As JHU explained, the Supreme Court and Federal Circuit have expressly held that public uses, sales, and offers for sale can be negated as §102 prior art if those activities were for experimental purposes. POR, 18-19. Those courts have not yet had the opportunity to specifically address negation of a printed publication made for experimental purposes.³ *But see Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 872 (3d Cir. 1977) (after prior use or sale is shown, “the burden shifts to the patentee to prove that any prior use, sale, or ***printed publication*** was for experimental, not commercial, purposes.”).

The logic and policy of experimental negation in the contexts of public uses, sales, and offers to sell apply equally to printed publications. As with an invention that requires public experimentation to establish usefulness, if a publication was made for purposes of experimentation—and indeed was ***necessary*** to enable the experimentation and to make the invention ready to patent—that publication should be negated as prior art, just as any experimental use would be negated.

³ This silence is unsurprising. The factual circumstances where an inventor must publish as part of his experimentation are limited. But the highly regulated area of human clinical studies can present exactly that circumstance.

Merck next criticizes FDA expert Jennifer Newberger by claiming she did not know what ClinicalTrials.gov required in 2013. Reply, 9. Not so. As Ms. Newberger explained immediately after Merck’s quote, the *statute*—as opposed to administrative guidance or the ClinicalTrials.gov website—*requires* the pertinent disclosures made in the MSR. EX1135, 242:16-243:3.⁴

Merck’s claim (Reply, 9-10) that the requirements of §101 and §112 do not preclude finding the MSR to be prior art is also wrong. The tension between the need to experiment to place an invention in patentable condition and the strictures of §102’s prior art provisions is long recognized. *See Pfaff*, 525 U.S. at 64-65. Merck’s cases fall far short of showing that it is “well established” that there is no requirement for human clinical trial data to meet the requirements of §101 and §112 for claims like these. Numerous cases have come out the other way, including one cited by Merck. *See, e.g., Balzarini*, 21 U.S.P.Q.2d at *6 (affirming rejection for lack of utility and non-enablement due to lack of human clinical data); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en

⁴ Merck’s footnote allegation (Reply, 9 n.15) regarding “inconsistent testimony” refers to an inconsequential inadvertent omission between declarations. *See* EX1242, 64:22-66:13.

banc); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). The uncertainty surrounding the amount of disclosure required to support patenting a method of treating human patients reinforces the importance of applying experimental-use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment.

C. Merck’s Identified Combinations Cannot Render the Challenged Claims Obvious

As JHU previously explained, Merck’s Petition failed to meet its burden on obviousness on multiple fronts, including because (i) Merck’s prior art (even in combination) does not disclose the “prior therapy,” “progressed,” “metastatic” or clinical outcomes limitations; (ii) Merck did not establish a reasonable expectation of success; and (iii) JHU’s significant objective-indicia evidence strongly supports non-obviousness. POR, 24-85. Merck’s Reply does not overcome these deficiencies.

1. Merck’s Obviousness Combinations Do Not Disclose or Render Obvious the Missing Limitations

Merck relies on circular reasoning to arrive at its conclusion that the combinations in Grounds 2 and 4 disclose the limitations requiring “prior cancer therapy drug,” “progressed...after the prior cancer therapy drug,” and “metastatic” cancer. Merck alleges that Benson teaches “clinical trials are only specified in the *standard of care* as therapy ‘after second progression’” (Reply, 14, original

emphasis), but this is only true for a subset of CRC patients who have advanced or metastatic disease (EX1009, 7). Merck thereafter (1) assumes cancer patients treated by the claimed method have *advanced or metastatic CRC*, which is *not* disclosed in the MSR and (2) ignores Benson’s repeated statement that “NCCN believes that the best management of *any* cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.” EX1009, 1-3; *see* POR, 25-26.

2. Merck Improperly Argues the Claimed Clinical Outcomes Are Inherently Disclosed

Merck’s prior art combinations do not explicitly disclose the clinical outcome limitations in Claims 1 and 3. POR, 26-31. Again, Merck must rely on an improper and unsupported inherency argument. Reply, 19-22; POR, 30-31. But “the use of inherency in the context of obviousness must be carefully circumscribed because that which may be inherent is not necessarily known and that which is unknown cannot be obvious.” *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (quotation omitted). Yet here, Merck does nothing more than cite its failed inherency argument—where the clinical results did not “inevitably flow” from the MSR (*supra* §II.A)—and rehash what it alleges a POSITA would understand from [REDACTED] the prior art. Reply, 19-22. None of this demonstrates that the clinical outcome limitations were

“necessarily known” in any of Merck’s obviousness combinations. Merck has not even attempted to meet that high standard; therefore, its inherent obviousness argument necessarily fails.

3. Merck Failed to Establish Reasonable Expectation that the Claimed Method of Treatment Would Succeed

Merck has now had multiple bites at the apple, but it still cannot articulate the correct standard for reasonable expectation of success (“RES”). First, Merck incorrectly argued that a POSITA “would have wanted to obtain the data from the MSI-H Study, including determining the outcome of patients.” POR, 31-32 (citing Pet., 39, 49-50); EX1003, ¶¶96-97, 101, 118-119, 125. After JHU pointed out that was the wrong standard (POR, 31-32), Merck pivoted, arguing that a POSITA would have had a RES in carrying out a generic two-step treatment method (Reply, 22-24). Critically, Merck’s generic method *leaves out the claimed clinical outcomes*, improperly lowering the bar for RES. Merck’s RES argument thus fails again.

Merck argues that JHU “misconstrues the [RES] standard by requiring a certain level of success and/or a certainty of success.”⁵ Reply, 23. Not true. JHU

⁵ Again, Merck mischaracterizes JHU’s argument regarding the MSS cohort. POR, 34-35.

applies the standard for RES laid out in the binding precedent of *OSI Pharmaceuticals v. Apotex Inc.* POR, 4, 15-16, 33-36, 38-39, 44-45, 47-48 (citing 939 F.3d 1375 (Fed. Cir. 2019)). In that case—that Merck fails to address—the Federal Circuit reversed the Board’s finding of unpatentability, holding that “hope that a potentially promising drug will treat a particular cancer is **not enough** to create a [RES] in a highly unpredictable art such as this.” 939 F.3d at 1385; *see* POR, 33-34.

Applying the correct standard, none of Merck’s evidence provides a RES for the claimed treatment method. It is undisputed that, as in *OSI Pharma*, the MSR does not disclose any efficacy data in humans or animals, or even any *in vitro* data. 939 F.3d at 1383. Each of Merck’s references provides only speculative statements, not clinical data, which Dr. Oberstein agreed would “be taken in a different light” than if a “definitive conclusion” were reached. EX2404, 124:3-14. For example, Pernot’s statement that MSI-H CRC patients could be “good candidates for immunotherapy” is facially speculative and limited to CRC. EX1006, 5; Pet., 37; Reply, 5, 24. As Dr. Oberstein testified, “immunotherapy” is a “very broad term” that could even include **exercise**. EX2404, 204:25-206:4.

Dr. Lonberg addressed each of Merck’s references and explained, “at best these references were inviting researchers to take an outside chance on investigating additional speculative hypotheses.” POR, 41-42 (citing EX2072,

¶¶154-157). Merck does not rebut Dr. Lonberg’s testimony. Nor does Merck rebut JHU’s evidence teaching away from the claimed treatment. *Id.*, 42-43. Merck’s contention that Dr. Lonberg and Dr. Goldberg “acknowledged” that “multiple prior art references suggested there were expected positive results for treating MSI-H tumors with PD-1 inhibitors” is flat wrong. Reply, 24. Merck ignores Dr. Lonberg’s testimony that JHU’s hypothesis was “not an anticipated outcome” and “does not imply any anticipation of – or any expectation of a particular result.” EX1245, 82:21-83:15; *see also id.*, 71:18-72:15; 80:22-85:7; 89:14-22. At best, Dr. Lonberg and Dr. Goldberg acknowledged (1) the public statements about BMS’s trial and (2) the scientific rationale included in the IND, which is not prior art.

Taken together, Merck’s evidence fails to demonstrate a RES in treating MSI-H CRC under *OSI Pharma*, let alone *all types* of MSI-H cancer, as required by the claims. *See* 939 F.3d at 1385.

4. Merck Failed to Rebut Much of JHU’s Objective-Indicia Evidence and Argument

a. Nexus

Merck provides no meaningful rebuttal to JHU’s evidence demonstrating that nexus should be presumed because the claims are co-extensive with Keytruda®’s label indication for treating MSI-H patients. POR, 51-59. For example, Merck’s Dr. Oberstein offers no opinion on nexus. EX2404, 240:14-

241:22. Nor does *any* Merck declarant provide an opinion identifying how the use of the product according to the label deviates from the claims.

Instead, Merck relies on a selective reading of JHU's declarant, Dr. Goldberg's deposition testimony.⁶ Reply, 25-26. The claims require a comparison between the outcome of a MSI-H cancer patient and the outcome of a "reference patient," i.e., a MSS cancer patient. EX1001, cl. 1. Merck claims "there is no legal or factual support to establish a presumption of nexus here based on the label." Reply, 26. But in doing so Merck ignores Dr. Goldberg's testimony on redirect, where he expressly revised his earlier testimony and agreed, upon further review, that the Keytruda® label did indeed instruct a physician to make the claimed comparison, consistent with his declaration. *See* EX1243, 128:18-130:19; EX2090, ¶¶91-92. And relying on the Keytruda® label is an appropriate

⁶ Merck's allegation that Dr. Goldberg "never used or followed the Keytruda® labeling when he treated MSI-H cancer patients" (Reply, 25 n.29), is undermined by the fact that Dr. Goldberg had personally stopped treating patients before the Keytruda® label contained the MSI-H indications (EX1243, 118:17-119:4), and that thereafter he supervised physicians who were administering Keytruda® "within the instructions of the KEYTRUDA label" (*id.*, 124:17-125:19).

way to connect the claimed method of treatment to the use of Keytruda®. *See, e.g., NuVasive, Inc. v. Iancu*, 752 F. App'x 985, 987 (Fed. Cir. 2018).

Merck's other nexus arguments also fall short. Merck implies that a presumption of nexus can only apply when a **product** is claimed, arguing that the '974 Patent is not a product patent. Reply, 25. But that is factually and legally unsound, as Federal Circuit precedent establishes that nexus can be presumed for method claims. *See, e.g., Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004) (“[N]exus may be inferred when...the thing (product **or method**) that is commercially successful is the invention disclosed and claimed in the patent.” (quotations omitted)); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020). The lone case that Merck cites for the contrary proposition provides no support, instead holding that nexus could not be presumed where there was an “extremely broad scope of the functionally claimed antibodies” as well as “unclaimed features that undisputedly materially affect” how a claimed product functions. *Teva Pharma Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1362-63 (Fed. Cir. 2021). Neither fact is alleged, let alone present, here.

Lastly, Merck falls back on its argument that nexus cannot be presumed because the claimed features were “indisputably known in the prior art.”⁷ Reply, 26. This circular argument necessarily fails because the claims are not anticipated, and because attorney argument alone cannot rebut the presumption of nexus. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328-29 (Fed. Cir. 2016).

b. Unexpected Results

Merck’s attempt to use [REDACTED] as evidence that the results of the claimed method were expected fails for at least two reasons. Reply, 27. First, it misrepresents [REDACTED]

[REDACTED] Moreover, Dr. Le testified that while the inventors were “hopeful,” they “certainly did not expect the outcome of [the] study to be as positive as it was.” EX2130, ¶27. Even if [REDACTED] did articulate an expectation of success, statements to FDA are *not public*—they were confidential and thus not prior art or within a POSITA’s knowledge.

⁷ While Merck’s rebuttal economics expert, Dr. Sheridan, references nexus in his declaration, he also bases his nexus opinion on a finding of anticipation. EX1151, ¶¶45-46.

That Merck and BMS had initiated similar clinical trials as of the Critical Date does not render JHU's results expected. As of the Critical Date, the only clinical data on treatment of MSI-H cancers was a single CRC patient. EX1057, 2-3; EX2176, 22; EX2072, ¶176; EX2090, ¶59. The BMS trial was limited to CRC, and the results were unknown. EX1053; EX2404, 286:25-287:12. Merck's trial is irrelevant, because it was "based on the encouraging results of [JHU's] early study." EX2061, 1; EX2404, 287:17-293:10. Moreover, Merck contemporaneously described JHU's results as "exciting, while early" and dMMR/MSI-H as a "*potentially* clinically meaningful tool." EX2061, 2.

Merck's cursory argument that JHU "incorrectly conflates degree of success with unexpectedness" also fails. Reply, 28. In Merck's *Hoffmann-La Roche Inc. v. Apotex Inc.* case, there was an otherwise clear showing of obviousness. 748 F.3d 1326, 1334 (Fed. Cir. 2014). Moreover, unexpected results are "useful to show the improved properties provided by the claimed [inventions] are much greater than would have been predicted," as is the case here. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quotations omitted).

c. Skepticism

Merck avoids addressing JHU’s skepticism evidence by improperly relying on hindsight, ignoring post-Critical Date evidence and criticizing JHU’s declarants.⁸

Merck concedes it provided no funding for JHU’s MSI-H study until after it knew the preliminary results. Reply, 28-29; *see also* EX1246, 108:8-112:16; EX1031, 10; EX1001, 21; EX2131, 8 (“No Funding shall be provided by Merck under this [2013] agreement.”). This contemporaneous evidence shows that Merck was skeptical of JHU’s hypothesis and only had a change of heart when preliminary results were published. This is telling evidence of nonobviousness. While Merck notes it provided its “expensive” drug, notably absent is any evidence of Merck’s cost for supplying it or any explanation for why this rebuts skepticism. Reply, 28-29.

⁸ Merck improperly relies on arguments it made in IPR2024-00240. Reply, 27, 28. To the extent the Board permits Merck to incorporate those arguments—it should not—JHU’s response to those arguments in its IPR2024-00240 Sur-reply should likewise be considered incorporated here.

Nor does Merck address or rebut the contemporaneous evidence that shows that even *after* JHU presented the MSI-H study results at ASCO and published them in NEJM, some researchers remained skeptical. Dr. Le recounted her experience at a January 2016 conference, where an audience member publicly criticized her because “it was too early for [her] to be presenting [their] data.” EX2130, ¶50. This skepticism in the field occurred well after July 10, 2015.

Regarding the statements by a Merck executive years later, Merck does not dispute that its executive said that “the idea was, early on” that anti-PD-1 agents (like pembrolizumab) “really [weren’t] going to work” in CRC. POR, 66-67; EX2121, 17. Instead, Merck argued this belief was “*prior* to the Parties’ collaboration[.]” Reply, 28-29. But that is exactly the point—before JHU’s unexpected clinical trial results, Merck was skeptical the claimed method would work.

Merck’s criticisms of JHU’s declarants fail. Merck takes aim at inventor Dr. Le for not remembering names of Merck employees from a decade ago. Reply, 7. But this minor point does not undermine Dr. Le’s testimony, and in any event, Merck provides no evidence rebutting Dr. Le’s testimony. As to BMS’s skepticism, JHU’s expert Dr. Lonberg testified firsthand that he thought the trial was “very risky” and noted that, ultimately, “the skepticism among decisionmakers

within [BMS] prevailed” regarding BMS’s rejection of JHU’s offer to join the MSI-H study. EX2072, ¶187. Merck has not demonstrated otherwise.

d. Long-Felt, Unmet Need

Before the Board, Merck contends that there was no unmet need for treating MSI-H patients before the Critical Date. Reply, 30-32. During the approval process, however, [REDACTED]
[REDACTED] EX2173, 17;
see also EX2170, 5 [REDACTED]
[REDACTED]; EX2171, 11,15, 18-20, 30, 32, 36-37; EX2172, 29; EX2167, 8-9; EX2173, 17; EX2174, 4-5. Merck ignores these statements and instead argues that FDA approval is not required by the claims. But that does not diminish the point—an unmet need clearly existed. Reply, 30-32, n.33; *see also* EX1243, 104:11-16. To make matters worse, Merck withheld its statements from its own expert, Dr. Oberstein (EX2404, 84:3-86:5), who readily admitted that as of the Critical Date, “MSI-high colorectal cancer patients did qualify as a high unmet need” (*id.*, 315:19-316:8). In other words, ***before this dispute***, Merck recognized and understood the unmet medical need for better treatments for MSI-H cancer patients. But Merck ***now*** casts this evidence aside with a perfunctory footnote (Reply, 30, n.33), obscuring the fact that Merck now asks the Board to draw the ***opposite*** conclusion.

In another attempt to distract from the clear unmet need here, Merck asserts that its patents “cover[] its drug and its use broadly in the treatment of cancer.” Reply, 30. This is conclusory and unsupported—neither Merck nor its experts analyze what these patents cover or any potential blocking effect. Further, so-called “blocking patents”—without more—do not undermine objective indicia of non-obviousness. *See Acorda Therapeutics, Inc. v. Roxane Lab ’ys, Inc.*, 903 F.3d 1310, 1338 (Fed. Cir. 2018). Moreover, Merck itself was certainly not blocked from solving the unmet need of treatments for MSI-H patients, yet it did not.

Merck’s “long felt need” for “an FDA-approved method” argument (Reply, 30-31), similarly falls flat. Far from “reveal[ing]” his view that the long-felt need was for an FDA-approved method—an opinion that appears nowhere in his declaration or in JHU’s briefing—Dr. Goldberg simply answered Merck’s question that used the words “FDA approved.” EX1243, 98:8-11; *see also* EX2090, ¶¶74. Notably, and perhaps intentionally, Merck did not ask Dr. Goldberg whether a long-felt need existed *more broadly* than just for an FDA-approved treatment. Without that question, Merck cannot draw its desired conclusion. Here, Dr. Goldberg simply relied upon the Keytruda® label—that ultimately resulted from FDA approval—to demonstrate the complete coextensiveness between the claimed invention and how Merck instructs doctors and patients to treat MSI-H cancer—i.e., according to the ’974 Patent claims. EX2090, ¶¶89-92.

Additionally, Merck's contention that the unmet need has no nexus to the claims is undermined by Merck's cited cases. Reply, 30-31. In both cases⁹, the Board found no long-felt unmet need existed because petitioners showed that known therapies in the art were treating patients *with similar efficacies* as the claimed therapies. Not so here. Before Keytruda®'s approval in 2017, the 5-year overall survival rates for patients with advanced disease were generally *less than 10%*. EX2090, ¶¶36, 50; EX2113; EX2114. Thus, clearly the 2013 MSR posting had not met this need. Treatment with the claimed method, however, resulted in a five-year overall survival rate of *50.3%* in non-CRC MSI-H patients and *57.5%* in CRC MSI-H patients, meaning *over half* of the patients were still alive *five years* after their initial treatment—an unprecedented increase in life expectancy. EX2090, ¶¶45, 50. And several patients experienced full remission beyond ten years. *Id.*, ¶¶71-74.

Finally, despite Merck's insinuation (Reply, 31-32), long-felt but unmet need does *not* require a separate showing of failure of others. *Millennium*

⁹ *Amerigens Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 86 (P.T.A.B. Jan. 17, 2018); *Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.*, IPR2015-01780, Paper 70 (P.T.A.B. Feb. 23, 2017).

Pharms., Inc. v. Sandoz Inc., 862 F.3d 1356, 1369 & n.5 (Fed. Cir. 2017). Even so, the abysmal overall survival rates for metastatic cancer patients, including MSI-H patients, as of the Critical Date plainly demonstrate a failure in the industry to meet this need.¹⁰

e. Industry Praise

Merck dismisses JHU's extensive evidence of industry praise (POR, 61-66) in a single paragraph focused on nexus (Reply, 32-33), ignoring the direct connection between JHU's evidence and the claimed invention. Dr. Le's presentation was touted for the key component of the claimed invention, i.e., "the identification of the first genomic marker [MSI-H]" to "predict the clinical benefit" of pembrolizumab. EX2135, 1. Dr. Le's presentation, simultaneously published in the NEJM (EX1031), is directly connected to the '974 Patent, which includes large portions of the article. EX1001. Further, Merck explicitly relied on Dr. Le's results to support the Keytruda® indication for treating MSI-H cancer.

¹⁰ Observing a complete response in a single CRC patient who was later identified as MSI-H, amid failures in every other CRC patient, does not satisfy a long-felt need. *See* Reply, 32 n.34. The reason for that complete response was unknown until JHU conducted its clinical trial.

EX2129, 74 (citing KEYNOTE-016/NCT01876511). Merck praised the JHU inventors’ “important scientific work” in the context of announcing that “*first-of-its-kind*, tumor-agnostic, indication.” EX2060, 2.

In the only cursory acknowledgement of JHU’s evidence, Merck criticizes Dr. Le’s testimony regarding her plenary presentation at ASCO as a “self-referential commendation.” Reply, 32 n.35. But Dr. Le’s statements are not in a vacuum—they are just the tip of the iceberg. Merck identified no evidence undermining the significance of Dr. Le’s ASCO presentation, let alone any of the other independent evidence of praise from the industry, FDA, and *Merck itself*. See POR, 61-66.

f. Commercial Success

Merck does not dispute that Keytruda® sales for the non-first line treatment of MSI-H patients grew after FDA approval for JHU’s patented treatment method [REDACTED] from 2017 to 2023. POR, 82-83; Reply, 33-35. Instead, Merck quibbles with the timing of an inflection point in sales, and comparisons of Keytruda® sales to competitor products. See Reply, 34. Merck misses the point. Merck’s estimated [REDACTED] in Keytruda® sales for non-first line treatment MSI-H patients *alone* is sufficient to prove commercial success. See POR, 83-84.

Merck’s other criticisms also fail. First, no Merck declarant provided any analysis of the “other patents” covering Keytruda® or their economic impact.

Reply, 33-34; EX1151, ¶¶31-34; EX2411, 23:4-11. “[T]he mere existence or sheer number of blocking patents does not, without more, necessarily detract from evidence of commercial success of a product or process,” *Acorda*, 903 F.3d at 1338 (internal quotations omitted). Even so, “[i]t is not necessary...that the patented invention be solely responsible for the commercial success.” POR, 85. Second, Merck is not an inventor on the ’974 Patent, so Merck is incorrect that “others” (here, JHU) were deterred from developing the claimed method. *See* Reply, 33-34. Third, Merck fails to explain how any of its criticisms would impact, if at all, Keytruda®’s commercial success in the MSI-H population. *See, e.g.*, EX2411, 53:21-54:3, 81:1-6; EX2191, ¶¶24-30. Instead, Merck continues to make significant sales that would not have been made ***but for*** JHU’s invention. *See* POR, 84-85.

Finally, Merck ignores that Mr. Segers evaluated Merck’s pricing and marketing—common economic factors that might affect commercial performance—to which Merck’s expert had no response. *See* EX2191, ¶¶38-44; EX2411, 53:21-54:3. Moreover, Merck failed to explain or quantify how any “brand recognition” would undermine Mr. Segers’ conclusion. *See* Reply, 34-35; EX2191, ¶¶24-30.

II. CONCLUSION

For these reasons, JHU respectfully requests the Board find the Challenged Claims patentable.

Respectfully submitted,

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CERTIFICATION UNDER 37 CFR § 42.24(d)

The undersigned hereby certifies that the word count for the foregoing
Patent Owner Sur-Reply totals 5,596 which is less than the 5,600 allowed under 37
CFR § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), the undersigned certifies that May 29, 2025, a complete and entire copy of this Patent Owner's Sur-Reply were provided via email, to the Petitioner by serving the email correspondence addresses of record as follows:

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