

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 IPR2024-00240
Patent 11,591,393 B2

PATENT OWNER'S SUR-REPLY

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LIST OF EXHIBITS

Exhibit Number	Description
2001	Declaration of Dr. Nils Lonberg
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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2011	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: Mar. 6, 2022) retrieved from File History of U.S. Patent No. 11,339,219 (U.S. Patent Application No. 17/131,328)
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2013	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: July 16, 2022) retrieved from File History of U.S. Patent No. 11,634,491 (U.S. Patent Application No. 17/739,278)
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2015	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: Dec. 17, 2021) retrieved from File History of U.S. Patent No. 11,649,287 (U.S. Patent Application No. 17/465,096)
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2032	NIH NATIONAL CANCER INSTITUTE, <i>What is Cancer?</i> (last updated Oct. 11, 2021), https://www.cancer.gov/about-cancer/understanding/what-is-cancer
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2037	Lotze et al., <i>Lysis of Fresh and Cultured Autologous Tumor by Human Lymphocytes Cultured in T-Cell Growth Factor</i> , 41 Cancer Research 4420-25 (Nov. 1981)
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2052	Declaration of Frank E. Scherkenbach in support of Motion for Pro Hac Vice Admission
2053	Declaration of Corrin N. Drakulich in support of Motion for Pro Hac Vice Admission
2054	Declaration of Dr. Christina D. Brown-Marshall in support of Motion for Pro Hac Vice Admission
2055	Declaration of Dr. Casey M. Kraning in support of Motion for Pro Hac Vice Admission
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2063	Thomson Reuters Streetevents, Edited Transcript MRK - Q4 2018 Merck & Co Inc Earnings Call, event date Feb. 1, 2019
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2069	Exhibit 12 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. 17-12 (D. Md. April 21, 2023)
2070	Statista, Leading drugs worldwide based on projected 2024 sales (in billion of U.S. dollars), released December 2023, available at https://www.statista.com/statistics/973523/top-drugs-by-year-on-year-sales-increase/
2071	Letter to Magistrate Judge Aslan from The Johns Hopkins University, Merck Sharp & Dohme LLC v. The Johns Hopkins University, Case No. 1-22-cv-03059-JRR, D.I. 100 (D. Md. May 14, 2024)
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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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2081	van der Bruggen et al., <i>A gene encoding an antigen recognized by 7cytolytic T lymphocytes on a human melanoma</i> , Science 254:1643-47 (Dec. 13, 1991)
2082	Lawrence et al., <i>Mutational heterogeneity in cancer and the search for new cancer-associated genes</i> , Nature 499:214-18 (July 11, 2013)
2083	Shigehisa Kitano et al., <i>Myeloid-derived suppressor cell quantity prior to treatment with ipilimumab at 10mg/kg to predict for overall survival in patients with metastatic melanoma</i> , J. of Clin. Oncology 30(15), 2518 (May 20, 2012)

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2102	Saltz et. al., <i>Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer, Irinotecan Study Group</i> , N. Engl. J. Med. 343(13):905-13 (2000)
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2106	Van Cutsem et al., <i>Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer</i> , N. Engl. J. Med. 360(14):1408-17 (Apr. 2, 2009)
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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)
2125	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Oct. 2015)
2126	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Aug. 2016)

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2127	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Mar. 2017)
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2129	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (June 2020)
2130	Declaration of Dung Le, M.D.
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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2147	42 C.F.R. Pt. 11 (2024)
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2149	Protocol Registration Data Element Definitions for Interventional and Observational Studies, Nat’l Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/policy/protocol-definitions

Exhibit Number	Description
2150	21 U.S.C. § 331 - Prohibited acts
2151	21 U.S.C. § 333 - Penalties
2152	De Angelis et al., <i>Clinical trial registration: a statement from the International Committee of Medical Journal Editors</i> , Editorial, Clinical Trial Registration (2004)
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Exhibit Number	Description
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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)
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I. INTRODUCTION

Recognizing that its Petition necessarily fails based on the absence of key disclosures in the MSR, Merck engaged a new, Merck-sponsored¹ oncology expert, Dr. Paul Oberstein, to offer opinions on Reply. But no amount of expert opinion or attorney argument can cure the deficiencies of the MSR reference. In the end, Merck remains unable to rebut JHU's arguments, including that: (1) the MSR does not disclose the "in response to" limitation because both MSS and MSI-H CRC patients were treated the same; (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 Merck's obviousness position.

Rather than rebutting JHU's arguments, Merck presents the Board with disingenuous interpretations of deposition testimony and allegations of contradictory statements to FDA and the Patent Office. Review of Merck's contentions reveals their falsity and highlights Merck's inability to prove any challenged claim unpatentable.

¹ Dr. Oberstein has received more than \$2.25 million in research funding from Merck. EX2404, 229:21-24.

II. “IN RESPONSE TO” IS A CAUSAL REQUIREMENT NOT TAUGHT BY THE MSR

Merck neither contests JHU’s construction of “in response to,” nor proposes its own construction. Both Merck and JHU *agree* that treating a patient “in response to determining” their MSI-H status requires a cause-and-effect relationship between determining the patient’s cancer is MSI-H and administering pembrolizumab. POR, 5-11; Reply, 8-10; EX1150, ¶21. The plain words of the claims, therefore, exclude administering pembrolizumab to patients determined to be MSS. Both parties took this position in district court. *See* EX2160, 30-31; EX2162, 22-23 (Merck arguing “the specification identifies a cause-and-effect relationship”). Both parties’ experts in this proceeding acknowledge that a causal relationship is required. EX2163, 70:25-71:2; EX2072, ¶¶84-85; EX1138, 120:15-122:4; EX1136, 196:3-197:1; EX2404, 247:23-250:10.

Unable to avoid the position it took in district court to avoid infringement liability, Merck argues here that JHU’s proposed construction amounts to an impermissible “attempt to insert” an “unclaimed negative limitation.” Reply, 9. Yet, unlike the cases Merck relies upon, the allegedly unclaimed “negative limitation” here is neither “unclaimed” nor “negative.” Rather, “in response to” is an affirmative recitation of which patients should be treated and which should not. *See Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir.

2011) (limitation requiring notification “in response to” vehicle conditions excludes notifications in response to user actions); *see also DoggyPhone LLC v. Tomofun LLC*, 2024 WL4848447, at *2-3, (Fed. Cir. Nov. 21, 2024) (limitation “begins transmission...in response to input from the pet” excludes transmission that begins when user clicks a notification); *Fujitsu Ltd. v. Belkin Int’l, Inc.*, 2012 WL4497966, at *27-30 (N.D. Cal. Sept. 28, 2012) (limitation requiring data transfer “in response to” receipt of the data excludes transfer requiring intervening user action); *Anylogic N. Amer., LLC v. THEBRAIN Techs., LP*, IPR2018-00546, Paper 10 at 10-14 (May 24, 2018) (limitation requiring displaying content “in response to” a first user interaction excludes displaying after multiple user interactions).

JHU’s construction of “in response to” is also consistent with the Summary of the Invention, which describes treating only patients determined to have MSI-H cancer while identifying MSS cancer as a “bad candidate for treatment with an immune checkpoint inhibitory antibody.” EX1001, 3:36-4:4; *see also id.* at 6:16-18, 13:24-26, 6:52-56, 5:45-53, 5:62-6:2. Construing the “in response to determining” step to include treating patients determined to have *either* MSI-H *or* MSS CRC would negate the limitation.

Merck's cited cases miss the mark. *Omega Engineering Inc. v. Raytek Corp.* is a pre-*Philips* case reversing a claim construction that violated a tenet of means-plus-function claim construction. 334 F.3d 1314, 1322 (Fed. Cir. 2003). In *Omega*, the Federal Circuit reversed the construction of "means for causing" a laser beam to strike the "periphery" of a zone that precluded the laser beam from striking the "center" of the zone, holding the "additional negative limitation finds no anchor in the explicit claim language." *Id.* There is no means plus function language at issue; here, the claim language allows treatment to be given only "in response to" determining the patient's CRC is MSI-H. This is not a negative limitation excluding treatment of MSS patients. In contrast, the MSR describes the same treatment protocol to be given to every CRC patient, regardless of MSI status, and not a disclosure of treatment "in response to" MSI-H determination as the claims require. EX2072, ¶¶94-101; EX2404, 283:21-284:10.

Merck's reliance on another pre-*Philips* case, *Renishaw PLC v. Marposs Societa' per Azioni*, is also misplaced. 158 F.3d 1243, 1250 (Fed. Cir. 1998). Merck relies on *Renishaw* (at Reply, 9) for the unremarkable proposition that "the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Id.* The inventors here invented a treatment method where MSI-H

CRC patients are treated with pembrolizumab and MSS CRC patients are not. The MSR's disclosure of treating **both** MSI-H and MSS CRC patients with pembrolizumab is **not** what the inventors "invented and intended to envelop with the claim." *Id.*

Merck also continues to conflate the MSR with the subsequent (non-prior art) clinical study, now arguing the MSR "is the written description support for the claims." Reply, 4, 9, 16. The written description support for the claimed method of treatment is not the MSR, but the **results** of the clinical study conducted pursuant to the MSR and its many subsequent amendments. *See* EX1001, Figs. 1-13. Indeed, in the MSR, MSI-H was **not** used as a "treatment selection marker" for CRC as contemplated by the '393 Patent. EX1001, 13:24-26. Only after the results of the clinical study were known was pembrolizumab approved to treat MSI-H CRC tumors, and used in practice as a treatment selection marker, as described and claimed by the '393 Patent.

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

A. The Challenged Claims Are Not Expressly Anticipated by the MSR

Merck's inability to show the MSR discloses the agreed causality requirement of the "in response to" limitation precludes its anticipation claim.

Pet., 21-23; Reply, 8-14; 37 C.F.R. §42.104(b)(4) (“The petition must specify where each element of the claim is found in the prior art...relied upon.”). Merck’s reliance on Dr. Oberstein’s opinions fails for the same reasons its previous reliance on Dr. Neugut’s opinions failed. Like Dr. Neugut, Dr. Oberstein opines the claimed causal relationship between MSI-H determination and treatment is disclosed simply because the MSI-H CRC patients were treated. EX1150, ¶¶64; EX2404, 251:3-253:18. This opinion, however, fails to confront the absence of a causal relationship required by the “in response to” limitation because the MSR discloses treating MSS CRC patients in the same manner as MSI-H patients. The MSR did not propose treatment of CRC based on a determination of MSI-H status, rather, it proposed treatment based on enrollment in the study. Dr. Oberstein ignores this critical distinction. EX1150, ¶¶61-69; EX2404, 251:3-253:18.

Rather than concede the MSR’s deficient disclosure, Merck misinterprets Dr. Lonberg’s testimony that scientists review the literature with a critical eye as willingly disregarding the teachings of the prior art. Reply, 3, 10-14. Merck ignores Dr. Lonberg’s explanation that a scientist would approach the prior art with “a questioning attitude toward it” and “would read it carefully and try to understand whether they – whether the assertions in the particular publication were justified.” EX1138, 85:2-86:5. Dr. Oberstein agreed with Dr. Lonberg’s approach,

admitting under oath, “I don’t agree with everything I read,” even in highly respected journals. EX2404, 117:9-118:14. Next, Merck attempts to justify the Board’s construction of “in response to” as meaning “after” by claiming it was altered by the Board’s single mention of a “causal relationship.” Reply, 1-2 (citing D.I., 16), 8-9. The Board’s reasoning illustrates that its mention of causality did not alter its construction, as it expressly disregards the enrollment and treatment of MSS CRC patients:

“At this point in the proceeding, Petitioner has sufficiently shown that there is a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of colorectal cancer patients and the determination of their MSI status — *all* colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were treated. *Whether or not other patients were treated or enrolled in the study does not detract from this teaching.*”

D.I., 15-16.² Making its position even clearer, the Board found, “[a]t this point in the proceeding, though, we do not interpret the claim step as *meaning anything other than* the treatment of colorectal cancer patients *after* they have been determined to be [MSI-H or dMMR].” *Id.*, 17. The rest of the Board’s analysis applies this construction, reading out the causation requirement that both parties agree must be present. *See Id.*, 15-19.

² All emphasis added, unless otherwise indicated.

Merck's Dr. Oberstein pays lip service to a causality requirement but ultimately uses the same flawed construction and reasoning. EX2404, 250:23-253:18 (“a subject would have to have MSI-high colorectal cancer and then be treated with an effective dose of pembrolizumab *after* determining that fact.”). Thereafter, Dr. Oberstein conceded the MSR proposes treating both MSI-H and MSS CRC patients in the same way. EX2404, 283:8-284:10. If the MSR requires treating MSS CRC and MSI-H CRC patients in the same way, the treatment cannot be “in response to determining that the colorectal cancer is [MSI-H]” as required by every claim of the '393 Patent. *See* §II above. Merck's anticipation argument cannot be saved by the Board's single mention of causality, which does not remedy the fact that the Board's construction of “after” expressly reads out the causation requirement Merck agrees is required. POR, 6-11; EX1150, ¶21.

B. Merck's Inherency Arguments Fail on Multiple Levels

Even if the MSR disclosed treatment of CRC “in response to” determining the patient is MSI-H—which it does not—Merck still must resort to multiple layers of inherency to fill other gaps in the MSR's disclosure. Applying the same Federal Circuit precedent on which Merck relies, Merck cannot satisfy the high bar for inherent anticipation.

First, Merck relies on inherency to supply multiple claim limitations missing from the proposed method of treatment disclosed by the MSR, including the requirements that the CRC patient “received a [different/prior] cancer therapy” and that the patient’s tumor “progressed [following/after]...[different/prior] cancer therapy,” (Pet., 25-27, 34; EX1003, ¶¶68-72, 93-94; EX1150, ¶¶75-78, 82; EX2404, 268:17-269:3); and the patient’s CRC was “metastatic,” (Pet., 31-33; EX1150, ¶¶83-87). Merck fails to make the requisite showing that these limitations were “necessarily present” in the MSR. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Merck’s expert admitted the MSR does not include enough information to rule out treatment of CRC patients who had not received a prior therapy. EX2404, 276:7-278:10. Merck’s expert also conceded that the MSR does not exclude treatment of non-metastatic, locally advanced CRC. EX2404, 272:17-276:6. If the MSR’s disclosure of treating patients meeting the required limitations is uncertain, then such disclosures cannot be “necessarily present” in the MSR.

Second, Merck relies on inherency to supply claimed outcome measures not disclosed by the MSR. In *In re Montgomery*, the Federal Circuit found that a clinical trial announcement may inherently anticipate a later method claim where 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 the same as the patent—the prior art MSR disclosure is not a part of the patent specification at issue, as was the case in *Montgomery*—and even if it were, the MSR does not disclose key limitations including the “in response to” requirement. Because the claimed method is different from the method disclosed by the MSR, the results claimed by the ’393 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 in the present case, i.e., “an invitation to investigate, [which] is not an inherent disclosure.” *Id.* at 1382 (citation omitted). JHU previously explained why the MSR was an “invitation to investigate.” POR, 26-29. Merck never addresses this critical point. Reply, 15-16. The investigative nature of the MSR is buttressed by JHU’s showing that: (1) the MSR is merely the first in a series of updated proposals for an experimental use designed to ready the invention for patenting (POR, 29-36); and (2) the Catch-22 Merck’s interpretation of inherency would create by forcing JHU to file a patent application before the clinical results were obtained for an invention for which “those of skill in the art

would not accept anything short of...human clinical trials.” *Ex Parte Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (B.P.A.I. 1991); POR, 36-38.

C. 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 provided data to support the '393 Patent's claims. JHU also provided un rebutted evidence demonstrating the applicability of the experimental use exception. *See* POR, 29-36. Merck 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 precisely the type of activity that courts have found support experimental use negation. The Board should find the MSR an experimental use disclosure.

Merck's bald declaration that JHU's position conflicts with the purpose of experimental use is wrong. *See* Reply, 17. The purpose of the exception is to allow “an inventor who seeks to perfect his discovery [to] conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye.” *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998). The MSR falls squarely within that purpose.

Merck also declares—again without analysis or elaboration—that the Board has found records posted on ClinicalTrials.gov to be printed publications.³ Reply, 17-18 (citing *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, No. IPR2022-00578, Paper 78 at 24-28 (P.T.A.B. Aug. 29, 2023) and *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024)). But neither panel addressed whether a ClinicalTrials.gov posting is subject to experimental negation. Because these panels were not presented with this issue, they cannot be said to have resolved it. *Cooper Indus., Inc. v. Aviall Servs., Inc.*, 543 U.S. 157, 170 (2004).

Finally, Merck criticizes FDA expert Jennifer Newberger in another failed effort to avoid the experimental use doctrine. Merck claims Ms. Newberger did not know what ClinicalTrials.gov required in 2013. Reply, 18. Not so. As Ms.

³ Merck’s footnote response to JHU’s cases, (Reply, 17 n.14), does not move the needle because the MSR was not a reduction to practice. *See infra* §III.D.2.b.

JHU was thus “free to experiment, test, and otherwise engage in activities to determine if the invention [was] suitable for its intended purpose and thus satisfactorily complete.” *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1357 (Fed. Cir. 2002).

Newberger explained immediately after Merck’s cherry-picked 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. Merck’s additional vague accusation that Ms. Newberger did not analyze all information in the MSR (Reply, 18) ignores that the information Ms. Newberger did not discuss in her thorough analysis concerned information not relevant to the ’393 Patent’s claims. *See* EX1135, 127:19-128:11, 250:18-253:20; EX1005, 3.

Merck’s claim (Reply, 19-20) that the requirements of §101 and §112 do not preclude finding the MSR to be prior art for the ’393 Patent is 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. 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. Numerous cases have come out the other way, including one cited by Merck. *See, e.g. Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (affirming claim 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 banc); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). The uncertainty surrounding the

amount of disclosure required to support a patent⁴ reinforces the importance of experimental use negation, especially in highly unpredictable fields such as cancer treatment.

Merck's final argument concerning Dr. Le's early observations of patient responses in JHU's clinical trial also does not change the calculus. Clinical trials are "powered" to include sufficient patients to establish the "likelihood that the response that you receive is actually an accurate response." EX2404, 203:22-204:21. Anecdotal, early observations are not sufficient for a study designed to enroll 71 patients and compare the results of MSI-H and MSS CRC patients. And, such observations certainly do not support claims to specific response rates. *See* EX1001, cls. 31-42.

⁴ Merck's acknowledgement of JHU's data-less first provisional (Reply, 19-20) reinforces this point. JHU understood even during prosecution that such a provisional could not support its claims. Yet Merck tries to use this application as a sword and a shield—in the Petition to prevent JHU relying on earlier priority date and in Reply to suggest that JHU knew it could receive its patents without data. Merck cannot have it both ways.

D. 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 “in response to” limitation; (ii) Merck did not establish a reasonable expectation of success; and (iii) JHU’s significant objective indicia evidence strongly supports non-obviousness. POR, 38-91. Merck’s Reply does nothing to address these deficiencies. For example, Merck does not dispute that it relies solely on the MSR as disclosing the “in response to” limitation. POR, 38-39. Because the MSR does not disclose this limitation, and Merck concedes none of the other references disclose it, Merck’s obviousness grounds necessarily fail. Merck also does not acknowledge, let alone rebut, its improper use of inherency to support its obviousness analysis. *Id.*, 39.

1. Merck Failed to Establish Reasonable Expectation That the Claimed Method of Treatment Would Succeed

As an initial matter, Merck does not address or rebut that it applied the wrong legal standard for reasonable expectation of success. *See* POR, 39-41 (Merck arguing that a POSITA “would have wanted to obtain the data from the MSI-H Study, including determining the outcome of patients.”) (citing Pet., 43,

45). Despite being on notice of this critical failing, Dr. Oberstein incorporated the same incorrect standard into his opinions. *See* EX1150, ¶¶136, 142.

Merck also fails to address the binding precedent of *OSI Pharmaceuticals v. Apotex Inc.*, where the Federal Circuit reversed a Board finding of unpatentability. *See* POR, 37, 41-47, 52 (citing 939 F.3d 1375 (Fed. Cir. 2019)). It is undisputed that, as in *OSI Pharmaceuticals*, the MSR does not disclose any efficacy data in humans or animals, or even any *in vitro* data. 939 F.3d at 1383. Merck's silence in the face of this precedential overlap is damning.

Merck's primary argument against JHU's reasonable expectation of success analysis is that JHU allegedly did "not take into account the state of the prior art as of the actual Critical Date." Reply, 20; *see also id.*, 24. Yet, 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" was reached. EX2404, 124:3-14. For example, Pernot's statement that "CRC associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy," is facially speculative. EX1006, 5; Pet., 43; Reply, 21. 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 the references on which Merck relies and explained that “at best these references were inviting researchers to take an outside chance on investigating additional speculative hypotheses.” POR, 48-49 (citing EX2072, ¶¶142-145). Merck does not rebut Dr. Lonberg’s opinion. Nor does Merck rebut JHU’s evidence teaching away from the claimed treatment. *Id.*, 49.

Merck makes much of Dr. Lonberg’s deposition testimony about the state of the art as of the Critical Date. Reply, 5; *see also id.*, 22. But Dr. Lonberg’s testimony was much more limited than Merck suggests.⁵ He either agreed that a document contained the words read by Merck’s counsel, (EX1138, 162:16-163:18, 165:16-166:12, 171:13-172:19, 180:7-182:13, 195:21-200:4, 203:13-208:3) or simply agreed to facts not in dispute:

- How MSI-H testing was performed. *Id.*, 48:16-52:3.
- CRC patients suspected of Lynch syndrome were routinely tested for MSI-H. *Id.*, 153:4-155:10.
- Bristol Myers Squibb (“BMS”) had announced a clinical trial for nivolumab. *Id.*, 175:12-19, 208:4-211:10.

⁵ Merck blatantly mischaracterizes portions of Dr. Lonberg’s testimony, highlighting the weakness of Merck’s obviousness case. *Compare* Reply, 22, with EX1138, 176:14-18.

- Pembrolizumab was known to be an immunotherapeutic administered intravenously. *Id.*, 175:20-176:1, 180:2-6, 182:14-183:16.
- A prior art reference overcome during prosecution of related patents showed an association between mutational load of tumors and susceptibility to PD-1 and/or PD-L1 inhibitors.⁶ *Id.*, 190:10-191:9.

None of these points satisfies Merck's burden to show that a POSITA would have expected that the specific study described in the MSR would succeed.

Merck points to BMS's initiation of a clinical trial in MSI-H CRC patients as evidence of a reasonable expectation of success. Reply, 21-22. Merck ignores that results from this trial were not available as of the Critical Date. EX2404, 286:25-287:12. That Dr. Lonberg had "expressed enthusiasm" about doing a similar study does not mean a positive outcome was reasonably expected, let alone certain.⁷ Reply, 21. As Dr. Oberstein conceded, the initiation of a clinical trial, even when based on preliminary clinical data, is no guarantee that the clinical trial

⁶ Notably, this reference disclosed 0% response rates in CRC patients. *See* EX1032, 2.

⁷ Nor does Dr. Goldberg's general statement about companies "aggressively researching immune-oncology opportunities," (Reply, 22) demonstrate a reasonable expectation of success.

will succeed. EX2404, 164:18-177:22; *see also* POR, 53-55. Nothing in the prior art at the Critical Date demonstrated BMS's trial would succeed. Reply, 21-23.

Equally reasonably, BMS was in a race with Merck for FDA approval of anti-PD-1 therapies (EX2051, 2, 7, 9, 11, 13-15) and perhaps feared losing ground on an MSI-H indication.

2. Merck Failed To Rebut Much of JHU's Objective Indicia Evidence and Argument

a. Nexus

Merck provides no substantive 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 CRC patients. Nor does Merck rebut JHU's evidence directly linking the evidence to the claimed invention. POR, 59-67. Merck's Dr. Oberstein offers no opinion on nexus. *See* EX2404, 240:14-241:22. Nor could Merck meaningfully rebut nexus, when its label for Keytruda® teaches the claimed method of treatment. Instead, Merck argues that the claimed features were known in the art.⁸ *See* Reply, 23. Merck's position necessarily fails

⁸ While Merck's rebuttal economics expert, Dr. Sheridan, references nexus in his declaration, he similarly bases his opinion on a finding of anticipation. EX1151, ¶¶40-41.

because the claims are not anticipated and because argument alone cannot rebut the presumption of nexus. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016).

b. Unexpected Results

Merck contends that JHU “utilizes the wrong time-period in its analysis” of unexpected results (Reply, 24), but Merck, not JHU, used the wrong date. “To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art *at the time of the invention.*” *UCB, Inc. v. Actavis Lab’ys UT, Inc.*, 65 F.4th 679, 693 (Fed. Cir. 2023) (internal citation omitted). The results of JHU’s clinical trial were announced by Dr. Le on May 29, 2015. EX2135; EX2061. These results were based on an analysis conducted as of May 8, 2015. EX2061, 2. The unexpectedness of JHU’s results should therefore be assessed as of May 8, 2015, when the invention was reduced to practice. Even if unexpectedness should be assessed as of July 10, 2015, the only non-anecdotal results available were the JHU inventors’ own results.

That Merck and BMS had initiated similar clinical trials as of the Critical Date does not render the JHU inventors’ results expected. Applying the correct

date, the only clinical data on treatment of CRC cancer with PD-1 inhibitors showed a 97% failure rate. EX1057, 2-3; EX2176, 22; EX2072, ¶166; EX2090, ¶52. The results of the BMS trial were unknown. *See supra* §III.D.1. Merck’s trial was not even initiated until May 29, 2015, so it is irrelevant. This is only logical, as Merck’s trial was “based on the encouraging results of [JHU’s] early study.” EX2061, 1; EX2404, 287:17-293:10. Moreover, Merck contemporaneously described the results as “exciting, while early” and dMMR/MSI-H as a “*potentially* clinically meaningful tool.” EX2061, 2.

Merck’s argument that “JHU’s analysis is undermined by its failure to compare the allegedly unexpected results with the closest prior art—the MSR” (Reply, 24), misses the mark. By its very name, a showing of unexpected results requires *actual results*. The MSR undisputedly contains no data, meaning the only comparison possible was against other studies with *known* results, and the available results of testing PD-1 inhibitors in CRC patients were bleak.

Merck’s argument about JHU inappropriately relying on the degree of success, rather than its unexpectedness, fails. Reply, 25. 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 *can* be “useful to show the improved properties provided by the claimed

[inventions] are much greater than would have been predicted.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

c. Skepticism

Rather than introduce any rebuttal evidence of its own regarding skepticism, Merck deflects and criticizes JHU’s declarants. For example, Merck takes aim at inventor Dr. Le, criticizing her for not remembering names of Merck employees from a decade ago, or for clarifying language in her declaration at Merck’s counsel’s behest. Reply, 6. But Merck provides no evidence rebutting Dr. Le’s testimony.

Further, Dr. Le’s “admission” that Merck provided funding for the clinical study (Reply, 6) falls flat; JHU has *never* contested that Merck provided funding *after* the study was underway. *See* POR, 74; EX1139, 67:13-73:15. Merck now baldly states that it had provided pembrolizumab, “along with funding, by the Critical Date” for JHU’s study. Reply, 27. Not so. Dr. Le, in the portion of her testimony that Merck cites as alleged support for its statement, describes how she could not remember the exact timing, only that it was “much later.” EX1139, 67:13-73:15. Merck and JHU’s agreement shows that [REDACTED]

[REDACTED] *See* EX2404, 306:19-307:21; EX2410, 3 [REDACTED]; *see*

also EX2131, 8 (“No Funding shall be provided by Merck under this [2013] agreement.”).

Merck’s 2013 decision to decline funding JHU’s study and present-day silence rebutting JHU’s skepticism allegation shows that Merck did not believe in the study in 2013, and only agreed to provide funding *after* the results were announced.⁹

d. Long Felt Unmet Need

Before the Board, Merck contends that there was no unmet need for treating MSI-H CRC patients prior to the Critical Date. *See* Reply, 28. During the approval process, however, [REDACTED]

[REDACTED]

EX2168, 10-13, 31; EX2169, 2 ([REDACTED])

[REDACTED]

[REDACTED]); *see also*

⁹ Merck’s criticism of Dr. Lonberg falls flat. Reply, 27. He testified from firsthand experience that he thought the trial was “very risky” and noted that ultimately “the skepticism among decisionmakers within [BMS] prevailed.” EX2072, ¶186. Merck has not shown otherwise.

EX2170, 5; EX2171, 11, 18-20, 30, 32, 36-37; EX2172, 29; EX2167, 8; EX2173, 17; EX2174, 4. Merck's argument that JHU failed to establish a long felt unmet need completely ignores its own statements to FDA. Reply, 27-29. To make matters worse, Merck withheld these statements from its own expert. EX2024, 84:3-86:5. Dr. Oberstein readily admitted that as of the Critical Date, "MSI-high colorectal cancer patients did qualify as a high unmet need." EX2404, 315:19-316:8. Before this dispute, Merck recognized and understood the long felt unmet medical need to find better treatments for MSI-H CRC patients, but now tells the Board a different story in attempt to paint JHU's invention as obvious.

Merck's arguments identifying alleged contradictions between JHU's statements to FDA and the Patent Office (Reply, 7, 22-23) are a smokescreen, as JHU provided the same information to both. For example, key portions of JHU's rationale to FDA appear verbatim in the '393 Patent. *Compare* EX1116, 39 *with* EX1001, 2:19-33. JHU's experts testified consistently. *See, e.g.*, EX2130, ¶¶9-10; EX2072, ¶57; EX2090, ¶¶53-54.

Merck's contention that JHU's evidence of long felt unmet need has no nexus to the claims is undermined by Merck's own cases. Reply, 27-28. In both

cases¹⁰, 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, the median overall survival for metastatic CRC patients on third-line therapy was *only 7 months*. EX2090, ¶45; EX2113; EX2114. But treatment with the claimed method resulted in a five-year overall survival rate of 57.5%, meaning over half of the patients were still alive *five years* after their initial treatment—an unprecedented increase in life expectancy. EX2090, ¶41. And several patients experienced full remission beyond ten years. *Id.*, ¶¶63-65.¹¹

¹⁰ *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).

¹¹ Despite Merck's insinuation (Reply, 29), long-felt unmet need does not require a separate showing of failure of others. *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 & n.5 (Fed. Cir. 2017). Even so, the abysmal overall survival rates for metastatic CRC patients point to a failure in the industry to meet this need.

e. Industry Praise

Because Merck has no cogent response to JHU's extensive evidence of industry praise, (*see* POR, 68-73), Merck dismisses it in a single paragraph. 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, 30 n.18. But Merck treats Dr. Le's statements as if in a vacuum, rather than as the tip of the iceberg. Merck's original expert explained that ASCO is "the super bowl of the cancer world," and Dr. Le's presentation "would be considered one of the main – one of the most important discoveries of the year[.]" EX1003, ¶35, n.1; EX2163, 107:4-12; *see also id.*, 106:4-107:3. 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 *even Merck itself*. *See* POR, 68-73.

f. Commercial Success

Merck does not dispute that sales of Keytruda® for the treatment of MSI-H CRC patients grew rapidly after FDA approval for JHU's patented treatment method. POR, 87; Reply, 30-33. Instead, Merck quibbles with the *rate* of growth and whether MSI-H CRC patients account for a "substantial portion" of Keytruda® patients. But neither is required. Merck's growing and significant

sales to MSI-H CRC patients alone is sufficient to prove commercial success. *See, e.g., Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999). Merck's expert agrees. EX2411, 71:4-8.

Merck's remaining criticisms also fail. First, Merck's expert provided no analysis of other patents purportedly covering Keytruda® nor their economic impact; and even so, "[i]t is not necessary...that the patented invention be solely responsible for the commercial success." *See* EX2411, 23:4-11; POR, 91. Second, Merck is not an inventor on the '393 patent, so Merck is incorrect that "others" (here, JHU) were deterred from developing the claimed method. *See* Reply, 31. Third, Merck fails to explain how any of its criticisms would impact, if at all, Keytruda®'s commercial success in the MSI-H CRC population. *See, e.g.,* EX2411, 53:21-54:3, 81:1-6; EX2191, 24-30. Merck continues to make significant sales that would not have been made but for JHU's invention. *See* POR, 86–90.¹²

¹² On nexus, Merck ignores Mr. Segers' testimony that Dr. Goldberg confirmed that sales for the MSI-H CRC indication could not have been made without practicing JHU's patented method. *See, e.g.,* EX1137 18:14-19:14, 133:22-134:8; 147:7-148:3, 150:7-14; 168:3-17.

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, 49:5-12. Moreover, Merck's expert failed to quantify any purported "halo effect" from other Keytruda® indications or "brand recognition" or explain how such an effect would undermine Mr. Segers' conclusion. *See* EX2191, ¶¶24-30.

IV. 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 5,600 allowed under 37 CFR § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on February 28, 2025, a complete and entire copy of this Patent Owners Sur-Reply was provided via email to the Petitioner by serving the correspondence address of record as follows:

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