



IPR2024-00240 Oral Hearing

March 31, 2025



Claim Construction

Importance of “In Response To”

- “In response to” is critical to JHU’s invention
- Merck’s Petition effectively ignores “in response to”
- Merck relies exclusively on the MSR as disclosing “in response to” for all grounds → If MSR does not disclose “in response to,” ***all grounds fail***
- Merck’s rebuttal to nexus turns on “in response to” being indisputably known

POR, 11–19, 38–39; Sur-Reply, 2–5, 19–20

Competing Constructions of “In Response To”

Board’s Preliminary Construction	JHU’s Proposed Construction
“after”	“in reaction to”
Merck’s Proposed Construction	Merck’s Previous Construction
None	“as the reaction specifically to”

DI, 16–18; POR, 5–11; Reply, 8–10; Sur-Reply, 2–5

Summary of Claim Construction Analyses

- JHU's Analysis
 - Claim language
 - Specification
 - Plain Meaning to POSITA
 - Examiner's interpretation ("Based on")
 - Dictionary definitions
 - Merck's previous construction ("As a reaction specifically to")
 - Federal Circuit precedent
- Merck's Analysis
 - Criticizes JHU's analysis of the Board's construction
 - Argues JHU's construction adds "unclaimed negative limitation"

POR, 5–11; Reply, 8–10; Sur-Reply, 2–5

Claims Differentiate “In Response To” And “After”

(10) **United States Patent**
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(54) **CHECKPOINT BLOCKADE AND MICROBIAL INSTABILITY**

(71) **Applicant:** **The Johns Hopkins University, Baltimore, MD (US)**

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1. A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising:

testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and **in response to** determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.

The claim language
itself differentiates
between “in response
to” and “after.”

7. The method of claim 1, wherein, prior to treatment with pembrolizumab, the patient had received a different cancer therapy, and the patient's cancer had progressed after the patient received the different cancer therapy.

20. The method of claim 14, wherein, prior to treatment with the step of selecting pembrolizumab for treating the patient's colorectal cancer, the patient had received a different cancer therapy, and the patient's cancer had progressed after the patient received the different cancer therapy.

EX1001 ('393 Patent)

Specification Discloses Treating MSI-H, Not MSS Cancers



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Diaz et al.

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
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6/34 (2013.01); C12Q 6/36 (2013.01); C12Q
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6/42 (2013.01); C12Q 6/44 (2013.01); C12Q
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6/62 (2013.01); C12Q 6/64 (2013.01); C12Q
6/66 (2013.01); C12Q 6/68 (2013.01); C12Q
6/70 (2013.01); C12Q 6/72 (2013.01); C12Q
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6/78 (2013.01); C12Q 6/80 (2013.01); C12Q
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6/86 (2013.01); C12Q 6/88 (2013.01); C12Q
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7/70 (2013.01); C12Q 7/72 (2013.01); C12Q
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7/78 (2013.01); C12Q 7/80 (2013.01); C12Q
7/82 (2013.01); C12Q 7/84 (2013.01); C12Q
7/86 (2013.01); C12Q 7/88 (2013.01); C12Q
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Plain Meaning to POSITA: Treat MSI-H, Not MSS Cancers

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021
Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. NILS LONBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/24 By: 
Nils Lonberg, Ph.D.

JHU 2072
Merck Sharp v. Johns Hopkins
IPR2024-00240

1

EX2072 (Lonberg Decl.), ¶ 85

85. Counsel has informed me and I understand that they propose that the Board interpret the term “in response to” as meaning “in reaction to.” I agree with this interpretation since it preserves the causal relationship embedded in the term “in response to,” and aligns with the purpose of the claimed method, which is to (1) identify CRC patients who are likely to respond to treatment with pembrolizumab and treat them and (2) identify CRC patients who are unlikely to respond to treatment with pembrolizumab and not treat them. I confirm that Counsel’s proposed construction is consistent with my analysis of the ’393 Patent in both the present declaration and my previously submitted declaration (EX2001).

POR, 10

Dictionary Definitions Support JHU's Construction

re·sponse (rĭ-spŏns') *n.* **1.** The act of responding. **2.** A reply or an answer. **3.** A reaction, as that of an organism or a mechanism, to a specific stimulus. **4a.** Ecclesiastical Something that is spoken or sung by a congregation or choir in answer to the officiating minister or priest. **b.** A responsory. [Middle English *respons* < Old French < Latin *respōsum* < neuter past participle of *respondēre*, to respond; see RESPOND.]

EX2153, 4

response (rĭ'spŏns) *n* **1** the act of responding; reply or reaction **2** bridge a bid replying to a partner's bid or double **3** (usually plural) Christianity a short sentence or phrase recited or sung by the choir or congregation in reply to the officiant at a church

EX2154, 4

response ► noun **1** a verbal or written answer: *there was laughter at his response to the question* | [mass noun] *we received 400 applications in response to one job ad.* ■ an answer to a question in a test, questionnaire, etc. ■ (usu. responses) a part of a religious liturgy said or sung by a congregation in answer to a minister or cantor. **2** a reaction to something: *an extended, jazzy piano solo drew the biggest response from the crowd* | [mass

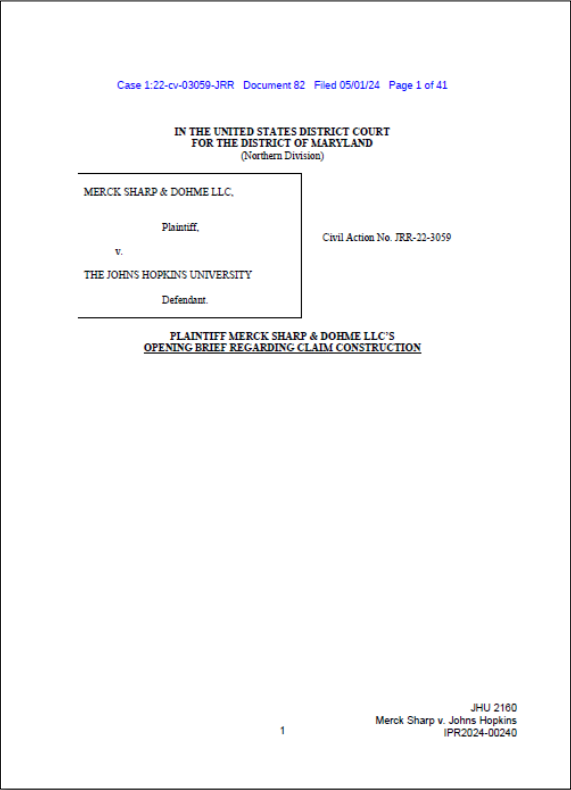
EX2155, 3

in /ɪn/ preposition; adv; adj
talks in a whisper. **RESULT** ► **10** ② used when referring to something that is done as a result of something else: *I'd like to do something for you in return/exchange for everything you've done for me.* • The changes are in response to demand from our customers. • He refused to say anything in reply to the journalists' questions.

EX2158, 3–4

POR, 10; EX2153–EX2159

Merck: “In Response To” Is “Reaction Specifically to a Stimulus”



EX2160 (Merck Op. Claim Construction Brief), 30–31

Merck’s Proposed Construction

“as the reaction specifically to”

The claim language in context requires that “treating” occur “in response to” some form of “determining.” The question for claim construction is, what does it mean, in the context of this medical treatment claim, for such treating to be in response to such determining. Scientific dictionaries are useful for understanding the meaning of “response” in this context—i.e., “a *reaction*, as that of an organism to any of its parts, to a *specific* stimulus.” (Ex. A-19 at 537 (2011) (emphasis added)). In this way, the response is a reaction specifically to a stimulus.

Merck Agrees MSI-H Is Determining Marker for Treatment

Case 1:22-cv-03059-JRR Document 82 Filed 05/01/24 Page 1 of 41

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
(Northern Division)

MERCK SHARP & DOHME LLC,

Plaintiff,

v.

THE JOHNS HOPKINS UNIVERSITY

Defendant.

Civil Action No. JRR-22-3059

PLAINTIFF MERCK SHARP & DOHME LLC'S
OPENING BRIEF REGARDING CLAIM CONSTRUCTION

1

JHU 2160
Merck Sharp v. Johns Hopkins
IPR2024-00240

*EX2160 (Merck Op. Claim
Construction Brief), 30–31*

This construction is consistent with the intrinsic record, which focuses on MSI-H as a determining marker for whether a cancer patient should be treated with pembrolizumab. For example, the specification explains that “[a]ny type of tumor that displays the MSI phenotype or a high mutational burden may be tested and/or treated according to the invention.” (Ex. A-5 at 6:16-18; *see also* Ex. A-5 at 13:24-26, 7:18-19, 6:52-56, 5:45-47, 5:51-53 (“The inventors have developed a treatment for cancer patients that display the microsatellite instability phenotype or other high mutational burden”), 5:67-6:2 (“Any tumors that are MSI or otherwise high may be treated according to the invention.”); Ex. A-19 at ¶¶ 19-22.)

JHU's Construction Does Not Add Negative Limitation



“We agree with the district court’s claim construction and its finding of prosecution history estoppel. ***‘In response to’ connotes that the second event occur in reaction to the first event. The language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction.*** Further, the specification fails to disclose any embodiment that requires any type of user interaction prior to identification of a service provider. See, e.g., ’928 patent, col.10 l.68–col.11 l.5. Thus, ***the court properly construed the claim terms ‘in response to’ and ‘when’ to require a cause-and-effect relationship.***”

Am. Calcar Inc. v. Amer. Honda Motor Co., Inc., 651 F.3d 1318, 1340 (Fed. Cir. 2011)

JHU's Construction Does Not Add Negative Limitation



“Honda’s accused system on the other hand requires a user to initiate a search for a provider by taking several steps. The user has not only to detect and select the message indicating that maintenance is required, but also has to select one of four options to ask the system to ‘Find Nearest Acura Dealer.’ Thus, ***when the user is presented with identification of the service provider, it is not ‘in response’ to the vehicle condition, as required by the claims, but rather, in response to user actions. ACI proposes that we ignore several intervening events that may or may not occur between the two relevant events. We are not persuaded to do so.***”

Am. Calcar Inc. v. Amer. Honda Motor Co., Inc., 651 F.3d 1318, 1340 (Fed. Cir. 2011)

JHU's Construction Does Not Add Negative Limitation

HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

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

IPR2024-00240
Patent No. 11,591,393

PETITIONER'S REPLY

Reply, 9

JHU's POR makes plain that it is asking the Board to require not just a causal relationship, but also "administering the claimed treatment *only as a reaction to* the determination that the patient's cancer is MSI-H." (POR, 8 (emphasis altered).) In other words, JHU advocates for a construction that excludes a treatment in which pembrolizumab is administered to patients that do not have MSI-H. Such unclaimed negative limitations should not be read into claim terms. See *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1322 (Fed. Cir. 2003) (rejecting the district court's "additional negative limitation" because it "[f]ound] no anchor in the explicit claim language").

Board's Preliminary Construction of "After" Does Not Reflect the Required Causation

Trials@uspto.gov
Tel: 571-272-7822

Paper 10
Entered June 13, 2024

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.

IPR2024-00240
Patent 11,591,393 B2

Before DEBORAH KATZ, ROBERT A. POLLOCK, and
DEVON ZASTROW NEWMAN, Administrative Patent Judges.

KATZ, Administrative Patent Judge.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

Paper 10 (DI), 15–16

At this point in the proceeding, contrary to Patent Owner's argument, Petitioner has sufficiently shown that there is a reasonable likelihood that the MSI-H Study Record teaches treating colorectal cancer patients after they were determined to be microsatellite instability high or DNA mismatch repair deficient with pembrolizumab. (See MSI-H Study Record, Ex, 1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); *see* Neugut Decl., Ex. 1003, ¶¶ 58–62.) 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.



No Anticipation By MSR (Ground 1)

Merck Failed to Show Anticipation

- MSR does not disclose:
 - “in response to”
 - “received a [different/prior] cancer therapy”
 - “progressed [following/after]...[different/prior] cancer therapy,”
 - Outcome measures (ORR, PFS, “shown in a clinical trial...”)
 - Metastatic CRC

POR, 11–25; Sur-Reply, 2–11

The MSR That Merck Relies On Is Not The Clinical Trial Itself

NIH U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01876511

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

[Latest version \(submitted February 4, 2020\) on ClinicalTrials.gov](#)

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
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- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in *red*.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	☒	☒	June 10, 2013	None (earliest Version on record)
2	☐	☐	June 12, 2013	Outcome Measures and Study Status
3	☐	☐	September 20, 2013	Recruitment Status, Study Status, Contacts/Locations and Oversight
4	☐	☐	May 21, 2014	Study Status and Conditions
5	☐	☐	June 25, 2014	Study Status, Contacts/Locations and Outcome Measures
6	☐	☐	September 15, 2014	Study Status and Contacts/Locations
7	☐	☐	December 26, 2014	Contacts/Locations and Study Status
8	☐	☐	January 29, 2015	Study Status and Contacts/Locations
9	☐	☐	February 26, 2015	Study Status and Contacts/Locations
10	☐	☐	April 15, 2015	Study Status, Contacts/Locations and Eligibility
11	☐	☐	June 9, 2015	Study Status, Eligibility and Study Design
12	☐	☐	January 4, 2016	Study Status and Eligibility

Page 1 of 6

MERCK EX1005

EX1005 (MSR), 4

NIH U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT01876511

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

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11	☐	☐	June 9, 2015	Study Status, Eligibility and Study Design
12	☐	☐	January 4, 2016	Study Status and Eligibility

MSR Does Not Teach “In Response To”

Merck’s Petition does not address “in response to.”

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

Patent No. 11,591,393

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,591,393

Pet., 21–23

The MSI-H Study Record is also enabled for the purposes of anticipation. In the context of treating cancer, “proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation,” and disclosure of the method enables the reference. *Rasmusson*, 413 F.3d at 1326. Here, as discussed above, the MSI-H Study Record discloses administering pembrolizumab 10 mg/kg every 14 days to colorectal cancer patients with MSI-H cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶59.)

POR, 16–19

MSR Does Not Disclose “In Response To”

History of Changes for Study: NCT01876511

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

[Latest version / submitted February 4, 2016 on ClinicalTrials.gov](#)

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11	☐	☐	June 9, 2015	Study Status, Eligibility and Study Design
12	☐	☐	January 14, 2016	Study Status and Eligibility

▼ Study Description

Brief Summary: This study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers.

Detailed Description:

EX1005 (MSR), 3

POR, 16–19; Sur-Reply, 2–8

MSR Does Not Disclose “In Response To”

- In MSR, MSI-H is *not a “treatment selection variable”* (specification) or a *“determining marker for whether a cancer patient should be treated with pembro”* (Merck) for CRC patients

History of Changes for Study: NCT01876511

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

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7	☐	☐	December 26, 2014	Contacts/Locations and Study Status
8	☐	☐	January 29, 2015	Study Status and Contacts/Locations
9	☐	☐	February 26, 2015	Study Status and Contacts/Locations
10	☐	☐	April 15, 2015	Study Status, Contacts/Locations and Eligibility
11	☐	☐	June 9, 2015	Study Status, Eligibility and Study Design
12	☐	☐	January 4, 2016	Study Status and Eligibility

EX1005 (MSR), 4

Arms and Interventions

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

POR, 16–19; Sur-Reply, 2–8

MSR Does Not Disclose “In Response To”

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021

Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. DUNG LE

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/2024 By: Dung Le Digitally signed by Dung Le
Date: 2024.10.04 11:39:22
+0800
Dung Le, M.D.

JHU 2130
Merck Sharp v. Johns Hopkins
IPR2024-00240

1

12. If our hypothesis was correct, we would see substantially more patients in the MSI-H CRC arm respond to treatment with pembrolizumab than in the MSS CRC arm. If our hypothesis was wrong, we would see no responders in either arm (as in the prior nivolumab studies) or a similar number of responders in both arms. If our hypothesis was wrong, we likely would have concluded that the anomalous response previously seen in the one colorectal patient was not tied to his MSI-H status.

EX2130 (Le Decl.), ¶ 12

POR, 16–19; Sur-Reply, 2–8

MSR: Same Treatment For MSI-H and MSS CRC Patients



EX2404 (Oberstein Dep.),
283:21–284:10

- Q. Okay. So let's assume that you have a colorectal cancer patient who is MSI-high and who is enrolled in Arm 1 of the proposed clinical trial, how would that patient be treated??
- A. So in the arms of intervention section of the clinical study record, it says that: Expect numbers, that the MSI positive colorectal cancer patient would be treated NK3475, which is pembrolizumab, milligrams per kilogram every 14 days.
- Q. Let's assume that you have **a colorectal cancer patient who is MS stable**, so not MSI-high, and who is enrolled in Arm 2 of the proposed clinical trial, **how would that patient be treated?**
- A. So in the same table, **an MSI negative colorectal cancer patient would be treated with MK3475, 10 milligrams per kilogram every 14 times.**
- Q. **And that's the same treatment as the MSI-high colorectal cancer patient enrolled in Arm 1; correct?**
- A. **That is correct. It's called MSI positive in this table, but yes.**

MSR Does Not Inherently Disclose Other Limitations

- Merck relies on inherency for multiple limitations
 - “received a [different/prior] cancer therapy”
 - “progressed [following/after]...[different/prior] cancer therapy,”
 - Outcome measures (ORR, PFS, “shown in a clinical trial...”)
 - Metastatic CRC
- Merck provides ***no evidence, opinion or argument*** that these limitations are “necessarily present”

POR, 19–29; Sur-Reply, 8–11

Inherent Disclosure Requires “Necessarily Present”



“[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is ***necessarily present***, or inherent, in the single anticipating reference.”

Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1377 (Fed. Cir. 2003)

POR, 27–29, 38–39; *Sur-Reply*, 8–9

Prior Therapy & Progression Not Necessarily Present in MSR

HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

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

Patent No. 11,591,393

REBUTTAL DECLARATION OF PAUL E. OBERSTEIN, M.D.

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MERCK EX1150
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00240

72. Therefore, the person of ordinary skill would have understood that treating patients who had received prior/different cancer therapies, and the patients' cancer had progressed after the patients received the different cancer therapies was found in the MSI-H Study Record.

EX1003 (Neugut Decl.), ¶ 72

POR, 25–29; Sur-Reply, 8–9

Prior Therapy Not Necessarily Present in MSR



EX2404 (Oberstein Dep.),
277:2–278:10

- Q. Okay. So *a patient who had an allergy to the available chemotherapy would not be excluded from the clinical trial proposed in Exhibit 1005?*
- A. *So there is not enough information in this trial to say whether that person would be included or excluded.*
- Q. But there is nothing in Exhibit 1005 that explicitly excludes someone who had refused chemotherapy because of an allergy?
- A. So I would say for a person of ordinary skill in the art, we would generally not accept a patient on a clinical trial because they, quote, refused chemotherapy. It would only be appropriate if they could not receive the chemotherapy because of an allergy or some other life-threatening condition.
- Q. But *that patient who is otherwise qualified under the inclusion and exclusion criteria in Exhibit 1005 would not be excluded from this clinical trial if they had not received a prior therapy because of an allergy to the available chemotherapy?*
- A. *So I don't think a POSA can determine if that person was excluded or based on what's available in 1005.*
- Q. Why not?
- A. Because *it does not speak to that point.*

Sur-Reply, 9

Metastatic CRC Not Necessarily Present in MSR

HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
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Patent Owner

Patent No. 11,591,393

REBUTTAL DECLARATION OF PAUL E. OBERSTEIN, M.D.

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MERCK EX1150
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00240

85. I agree with Dr. Neugut that in the context of the MSI-H Study Record, where the underlying phase 2 clinical study involves a new immunotherapy drug, the POSA would understand that the MSI-H Study Record requires that the colorectal cancer patients being treated have metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure.

EX1150 (Oberstein Decl.), ¶ 85

Sur-Reply, 9

Metastatic CRC Not Necessarily Present in MSR



EX2404 (Oberstein Dep.),
274:16–275:6

- Q. So there is some group of nonmetastatic colorectal cancers that a person of ordinary skill would expect would be able to be enrolled in the clinical trial proposed by Exhibit 1005?
- A. So I think that ***a person of ordinary skill would have to evaluate a locally advanced nonmetastatic patient who has already received and progressed in prior therapy to determine if they would be suitable for the trial*** based on their other treatment options and whether this was possible.

Sur-Reply, 9

Montgomery Test Is Not Satisfied



**“The *inherent result must inevitably result from the disclosed steps*;
“[i]nherency ... may not be established by probabilities or possibilities.”**

In re Montgomery, 677 F.3d 1375, 1380 (Fed. Cir. 2012)

Sur-Reply, 9–11

Montgomery Test Is Not Satisfied

MSR

Method

Both MSI-H and
MSS CRC
Treated

Requires only
“measurable”
cancer

No mention of
prior therapy or
progression

Results

None

Claimed Method

Method

Treatment Only
In Response to
MSI-H
Determination
Prior therapy*
Progression*
Metastatic CRC*

Results

MSI-H Validated as
Treatment Selection
Variable

Amount of Pembro
shown in clinical trial
to be effective at
promoting PFS

ORR 40% or higher

PFS of at least 78%
(20 weeks) or 60% (9
months)

*Dependent Claims

POR, 25–29; Sur-Reply, 8–11

Montgomery Is Distinguishable



“In all relevant respects, HOPE is identical to the patent itself, which does not disclose actual results from the administration of ramipril for these purposes. Montgomery conceded at oral argument that HOPE’s authors could have obtained the patent claims at issue based the HOPE reference, so it cannot be that this reference fails to anticipate.”

In re Montgomery, 677 F.3d 1375, 1383 (Fed. Cir. 2012)

POR, 25–29; *Sur-Reply*, 8–11

Montgomery Is Distinguishable



“To be sure, as the dissent points out, “[a]n *invitation to investigate is not an inherent disclosure.*” *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004). But **HOPE’s protocol** for the administration of ramipril **is far from an abstract theory—it is an advanced stage of testing designed to secure regulatory approval.** HOPE was designed to obtain data for submission to regulatory agencies on the effect of ramipril on cardiovascular diseases including stroke **based on substantial evidence** that ramipril improved cardiovascular health, including by treating stroke risk factors such as hypertension.”

In re Montgomery, 677 F.3d 1375, 1382 (Fed. Cir. 2012)

POR, 25–29; *Sur-Reply*, 8–11

MSR Was An “Invitation to Investigate”

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT01876511

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

[\[Latest version / Submitted February 4, 2016 on ClinicalTrials.gov\]](#)

A study version is represented by a row in the table.

Select two study versions to compare. One each from columns A and B.

Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.

Click "Compare" to do the comparison and show the differences.

Select a version's Submitted Date link to see a rendering of the study for that version.

The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.

Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study edits or deletions are displayed in red.

Study additions are displayed in green.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	☒	☒	June 10, 2014	None (earliest version on record)
2	☐	☐	June 10, 2014	Outcome Measures and Study Status
3	☐	☐	September 26, 2014	Recruitment Status, Study Status, Contacts/Locations and Oversight
4	☐	☐	May 21, 2014	Study Status and Conditions
5	☐	☐	June 26, 2014	Study Status, Contacts/Locations and Outcome Measures
6	☐	☐	September 16, 2014	Study Status and Contacts/Locations
7	☐	☐	December 26, 2014	Contacts/Locations and Study Status
8	☐	☐	January 29, 2015	Study Status and Contacts/Locations
9	☐	☐	February 26, 2015	Study Status and Contacts/Locations
10	☐	☐	April 15, 2015	Study Status, Contacts/Locations and Eligibility
11	☐	☐	June 9, 2015	Study Status, Eligibility and Study Design
12	☐	☐	January 14, 2016	Study Status and Eligibility

Page 1 of 6

MERCK EX1005

EX1005 (MSR), 3

▼ Study Description

Brief Summary:

This study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers.

Detailed Description:

POR, 25–29; Sur-Reply, 8–11

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

36

JHU's Unrebutted Evidence of Invitation to Investigate

- JHU inventors' hypothesis based on **one** MSI-H CRC patient who responded to treatment with nivolumab
- Only study on PD-1 inhibitors (nivolumab) in CRC patients had a 97% failure rate
- No animal data to support hypothesis
- No patients enrolled or treated
- BMS and Merck skeptical of proposed trial

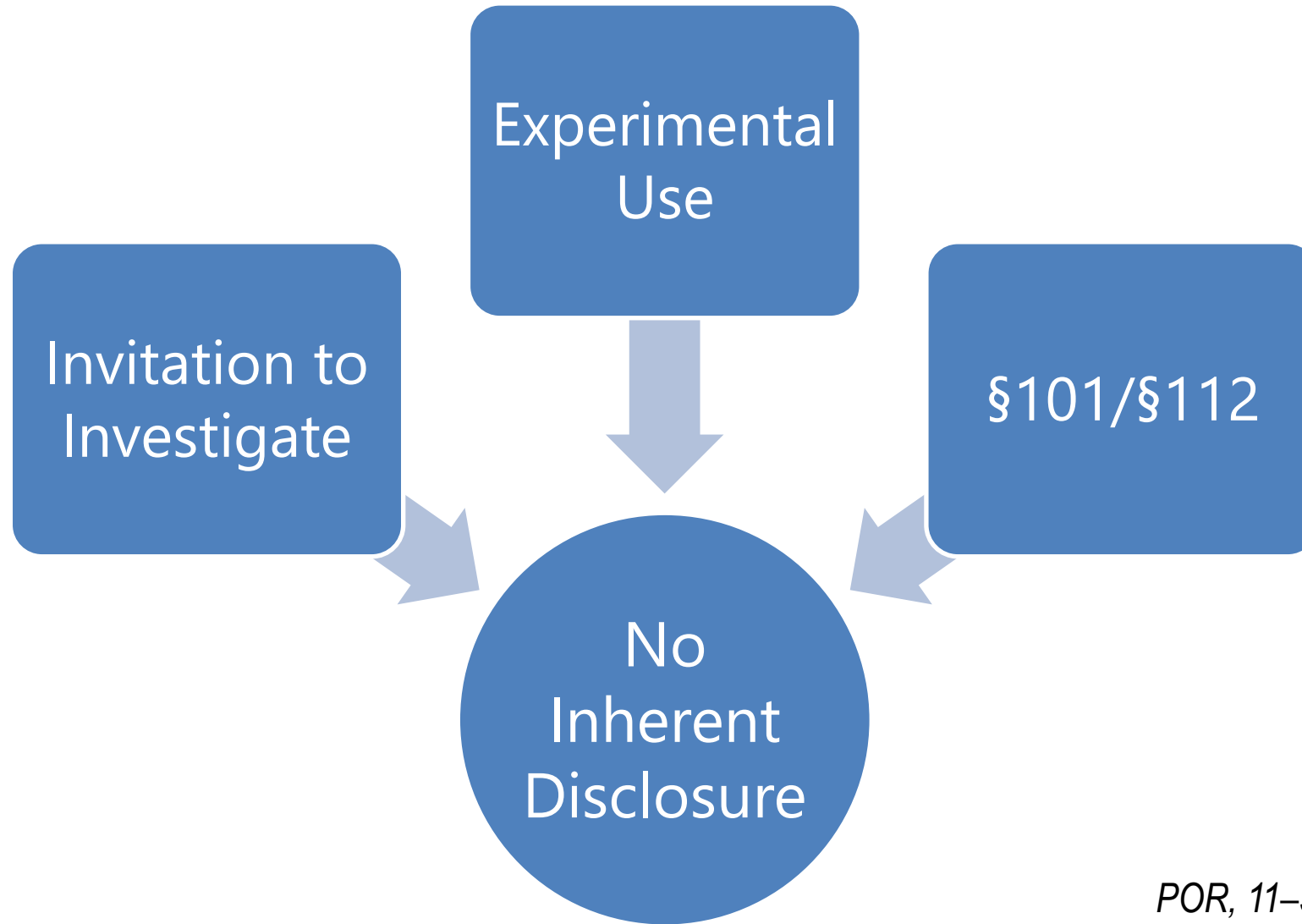
POR, 25–29, 43; Sur-Reply, 8–11

Montgomery Is Distinguishable

- No experimental use argument raised nor addressed
- *Montgomery* turned only, and entirely, on inherent anticipation

POR, 25–29; Sur-Reply, 8–11

MSR Does Not Inherently Disclose Outcomes



POR, 11–38; Sur-Reply, 5–15



MSR Was Proposed Experimental Use

JHU's Unrebutted Evidence of Experimental Use

- Necessity
- Control
- Nature of Invention
- Necessity of Testing Under Conditions of Use
- Length of Time
- No Payment or Commercial Exploitation
- Nature of Contacts with Potential Customers

- Secrecy Obligations
- Recordkeeping
- Who Conducted the Experiment
- Whether Testing Was Systematic
- Monitoring of the Experiment

POR, 29–36; Sur-Reply, 11–14

Purpose, Not Form, Defines Experimental Use

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 RESPONSE

HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

POR, 29–30

public eye.”). Consistent with these policies, the Supreme Court and Federal Circuit have held that public experimental activities can be negated as §102 prior art if those activities were for experimental purposes. See, e.g., *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 133-36 (1877) (discussing experimental negation of a public use); *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352-55 (Fed. Cir. 2002) (discussing experimental negation of sales and offers for sale); cf. *Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 872 (3d Cir. 1977) (“Once the party asserting invalidity has convincingly proven the prior use or sale... the burden shifts to the patentee to prove that any prior use, sale, or printed publication was for experimental, not commercial, purposes.”).



Obviousness Grounds 2–8 Fail

Merck Failed To Show Obviousness

1. Merck's prior art does ***not*** disclose “in response to”
2. Merck has ***not*** established a reasonable expectation of success
3. JHU has shown ***significant objective indica*** of non-obviousness

POR, 42–91; Sur-Reply, 15–28

Merck Relies on MSR *Alone* for “In Response To”

Ground	Claims	Secondary Reference(s)	Rationale
Ground 2	1 -2, 4-7, 11-12, 14 -15, 17-20, 24-25, & 27-42	Pernot	- Improved outcome/Efficacy - Testing for MSI-H
Ground 3	2, 8, 15, & 21	N/A or Pernot & Chapelle	Testing tumor tissue
Ground 4	3 & 16	N/A or Pernot & Steinert	Testing body fluid
Ground 5	7, 20, 29-30, 32, 34, & 36-42	N/A or Pernot & Benson	- Different cancer therapy prior to pembrolizumab - Patient’s cancer had progressed

Pet., 3–5, 42–63

Merck Relies on MSR *Alone* for “In Response To”

Ground	Claims	Secondary Reference(s)	Rationale
Ground 6	9, 10, 22, & 23	N/A or Pernot & Salipante	Testing for MSI-H via PCR or next generation sequencing
Ground 7	11-12 & 24-25	N/A or Pernot & Hamid	Routes of pembrolizumab administration
Ground 8	13 & 26	N/A or Pernot, Steinert, & Hamid	Routes of pembrolizumab administration

Merck Relies on MSR *Alone* for “In Response To”

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

Patent No. 11,591,393

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,591,393

Pet., 42–43

3. Ground 2: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the '393 Patent Are Obvious Over the MSI-H Study Record in View of Pernot

As discussed above, Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that (1) even if Patent Owner (erroneously) argues that the MSI-H Study Record cannot anticipate because it did not affirmatively disclose an improved outcome or that a POSA would not have expected such efficacy (EX1022, December 14, 2020 Notice of Allowance at 3; *see also supra*, §I; *infra*, §VII.B), and/or (2) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach “testing, or having tested, a biological sample obtained from a patient” as recited in the independent claims, Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42, would at a minimum still be unpatentable for obviousness in view of Pernot and the knowledge of a POSA.

Merck Relies on MSR *Alone* for “In Response To”



EX2163 (Neugut Dep.),
150:2–7, 151:2–9

Q. You are ***not relying on Pernot for disclosing the “in response to”*** claim limitation, right?

A. Correct.

POR, 38–39

Pernot Does Not Supply “In Response To”

- Pernot ***cannot*** and ***does not*** supply “in response to”
 - No disclosure of testing patients for MSI-H status
 - No disclosure of treating MSI-H patients with pembrolizumab
- A good candidate for “immunotherapy” does not mean treatment with a PD-1 inhibitor such as pembrolizumab ***in response to*** determining the CRC is MSI-H

POR, 38–39, 45–48; EX2072 (Lonberg Decl.), ¶¶ 71–73, 139–141; EX2163 (Neugut Dep.), 152:12–153:6

If MSR Does Not Disclose “In Response To,” All Grounds Fail

- If the Board determines that the MSR does not teach “in response to,” ***all Merck’s obviousness grounds fail***
- Merck relies solely on the MSR as disclosing “in response to.”

POR, 38–39, 45–48; Sur-Reply, 15; EX2072 (Lonberg Decl.), ¶¶ 71–73, 139–141; EX2163 (Neugut Dep.), 151:2-9



No Reasonable Expectation of Success

Correct Legal Standard for RES of Treatment Claims



It is “not enough for the [patent challenger] to have shown that a skilled artisan would have pursued the claimed method as a treatment option,” but rather the challenger “***also*** had to show that the skilled artisan would have reasonably expected to achieve ***success in the treatment.***”

Eli Lilly & Co. v. Teva Pharms. Int’l GmbH, 8 F.4th 1331, 1344 (Fed. Cir. 2021)

Facts for State of the Art and RES

- Cancer therapy is **unpredictable**
 - EX2072, ¶¶ 33–57, 113, 126
- **No animal models** of MSI-H cancer existed and no way to generate preclinical data
 - EX2163, 148:3–6; EX2072, ¶¶ 54–55, 115–116, 138, 188; EX2073, 3–4
- No PD-1 inhibitor had been approved for any indication before JHU's posting of the MSR on June 10, 2013.
 - EX2072, ¶¶ 113, 138
- MSI-H and MSI-stable patients were treated the same way and only ***retrospectively*** identified in cited clinical trials
 - EX2090, ¶ 33; EX1023; EX1016, 6–7; EX1017, 5–6; EX2072, ¶¶ 162–165

Hope is Not a Reasonable Expectation of Success



“[H]ope that a ***potentially promising drug*** will ***treat a particular cancer*** is not enough to create a reasonable expectation of success in a highly unpredictable art such as this.”

OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375, 1385 (Fed. Cir. 2019)

Only Reasonable Expectation Was Failure, Not Success



“Indeed, ***given a 99.5% failure rate*** and no efficacy data or any other reliable indicator of success, ***the only reasonable expectation at the time of the invention was failure, not success.*** It is ***only with the benefit of hindsight*** that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references.”

OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375, 1385 (Fed. Cir. 2019)

OSI Pharms. Dictates No RES Here

<i>Facts in OSI</i>	<i>Facts Here</i>
Method for treating non-small cell lung cancer (NSCLC) with erlotinib	Method for treating MSI-H colorectal cancer with pembrolizumab
None of Petitioner's references disclosed treatment of NSCLC with erlotinib	At the time of publication, no patient with a MSI-H tumor had been either enrolled or treated with pembrolizumab. EX2163, 136:24–137:6; EX2072, ¶138
The Board relied on a review article stating that erlotinib was in clinical trials and had “good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with” NSCLC and erroneously concluded that this was a “clear inference” that erlotinib had anti-cancer activity against NSCLC	Both experts agree that nothing in the MSR tells a POSA that the MSI-H status would indicate successful treatment of colon cancer. EX2163, 137:19–23; EX2072, ¶¶ 66–70, 111, 137–38, 172
No data or other information on erlotinib's efficacy in treating NSCLC	No efficacy data in humans or animals, or any <i>in vitro</i> data. EX2163, 148:3–6; EX2072, ¶¶ 54–55, 115–16, 138, 188
Highly unpredictable nature of treating NSCLC Over 99.5% failure rate of drugs entering Phase II	97% failure rate for another PD-1 inhibitor in BMS study. EX1002, 205; EX1057, 2–3; EX2176, 22; EX2072, ¶ 166; EX2090, ¶ 52.

MSR Does Not Support RES

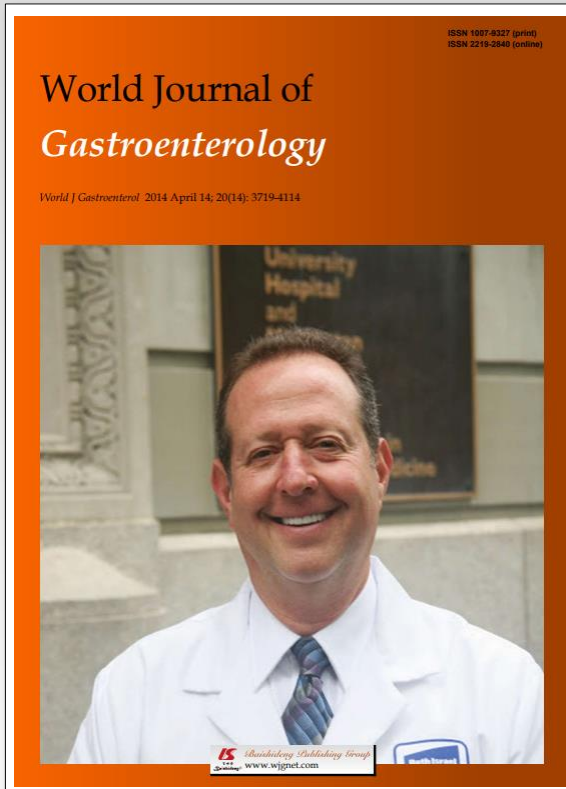


EX2163 (Neugut Dep.),
137:19–23

Q. Is there anything in the MSI high study record in Exhibit 1005 that tells a POSA that the protocol will be ***successful or have a positive outcome?***

A. ***No.***

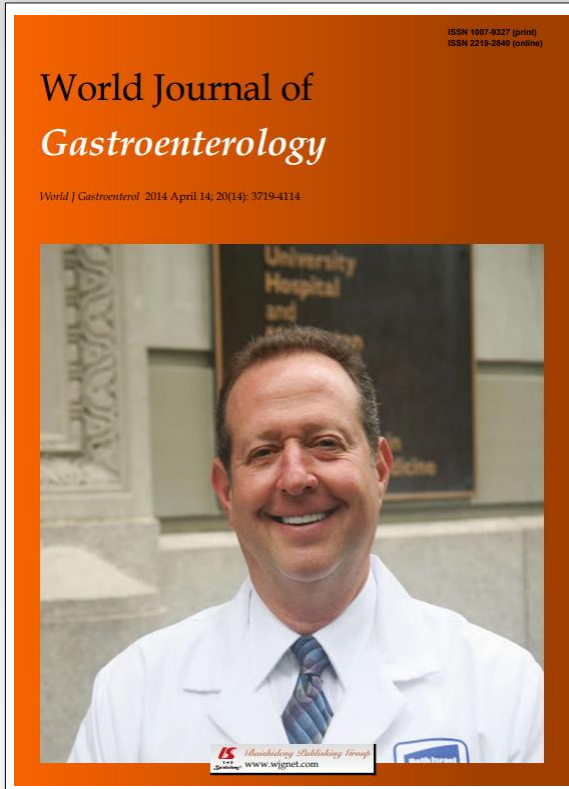
Pernot Provides Only Speculative Statements



EX1006 (Pernot), 5

increased lymphocyte infiltrate. These results suggest an important role of the immune response to specific neoantigens in CRC with MSI, and its potential involvement in the better prognosis of these tumors. Nevertheless, CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients^[31]. Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation^[32,33] though the association between HLA class I downregulation and MSI is still controversial. Altogether, CRC associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy.

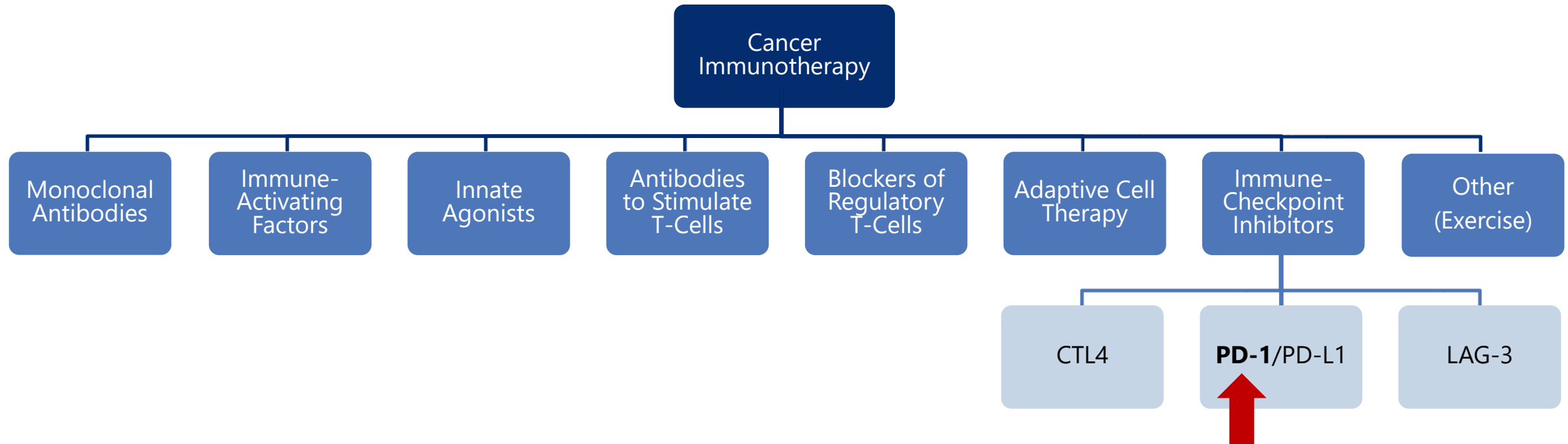
Pernot Provides Only “Hope,” Not RES



EX1006 (Pernot), 5, 9

- “CRC associated with MSI ***could*** lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good ***candidates for immunotherapy***”
- “immunotherapeutic approaches is a seducing ***alternative to try*** to improve the prognosis of these patients in the future”

“Immunotherapies” Much More Than Anti-PD-1 Therapies



POR, 46–47, 50: EX1006, 9; EX2072 (Lonberg Decl.), ¶¶ 44–48; Sur-Reply, 16; EX2404 (Oberstein Dep.), 204:25–206:3

“Immunotherapies” Much More Than Anti-PD-1 Therapies

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
 U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
 Issue Date: February 28, 2023
 Appl. Serial No.: 17/465,101
 Filing Date: September 2, 2021
 Title: CHECKPOINT BLOCKADE AND
 MICROSATELLITE INSTABILITY

DECLARATION OF DR. NILS LONBERG

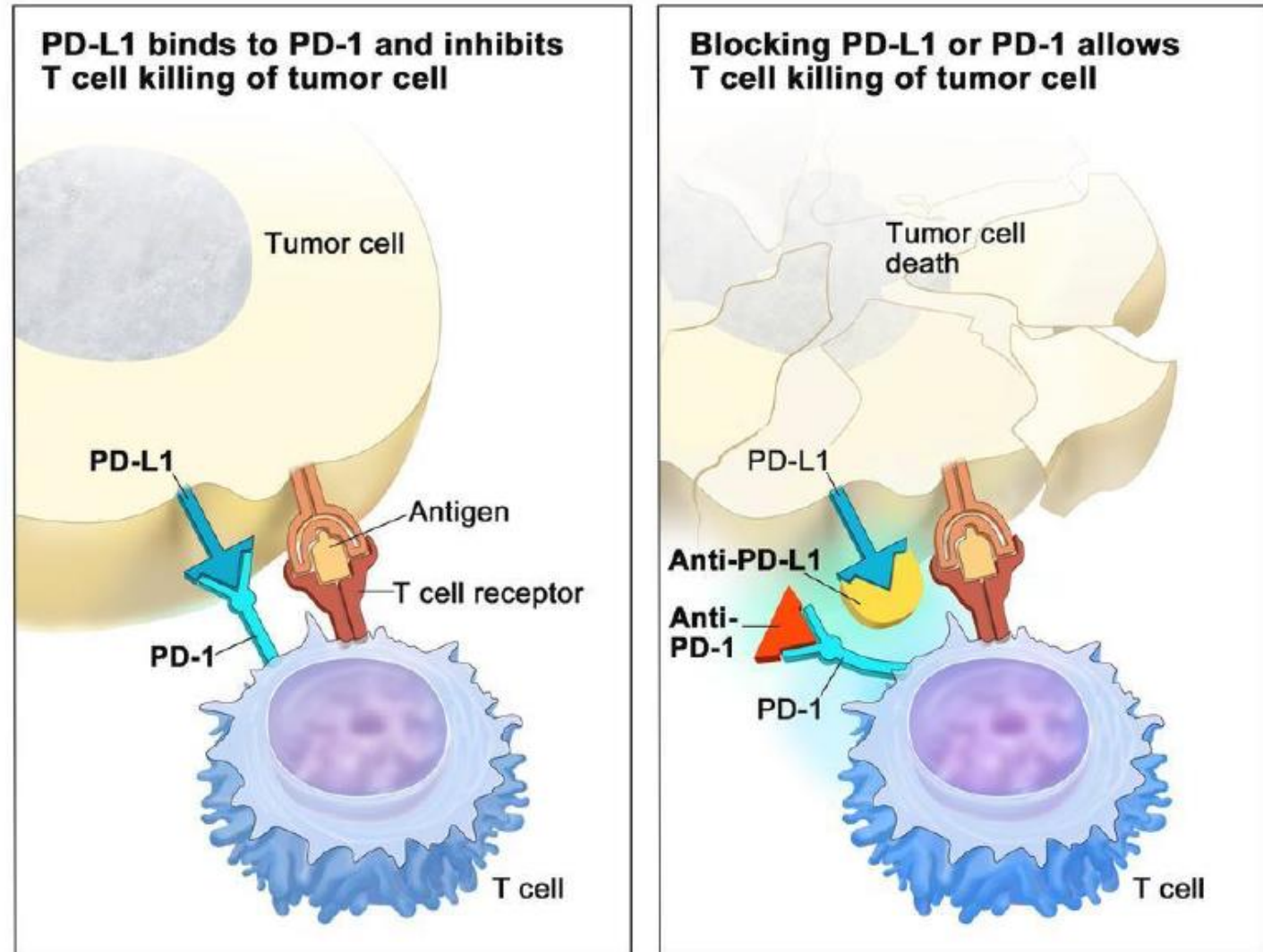
I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/24 By: Nils Lonberg, Ph.D.

JHU 2072
 Merck Sharp v. Johns Hopkins
 IPR2024-00240

EX2072 (Lonberg Decl.), ¶ 47



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“Immunotherapies” Much More Than Anti-PD-1 Therapies



EX2404 (Oberstein Dep.)

274:16–275:6

Q. What do you mean by “immunotherapies”?

A. So that in that sentence, I mean ***a very broad term of any therapy that modifies the immune system in order to affect cancer outcomes.***

Q. Okay.

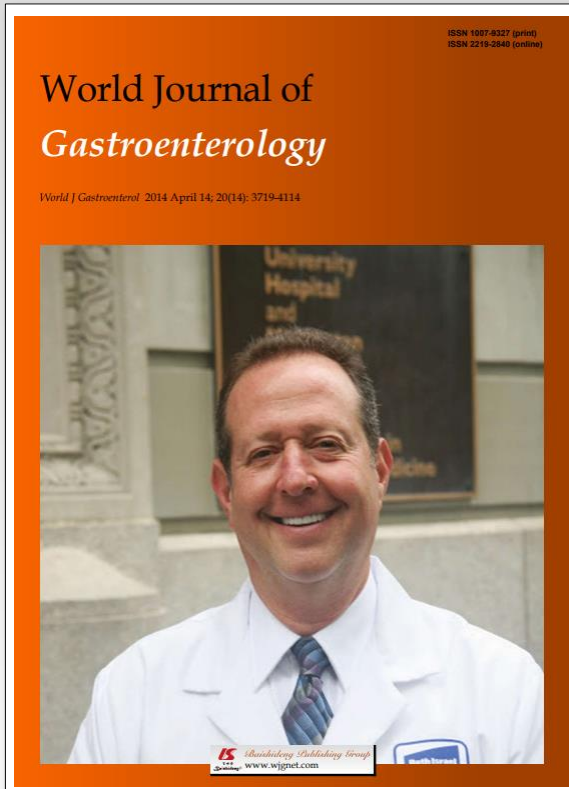
A. And so it can incorporate ***checkpoint therapies, other checkpoints besides the PD-1, PD-L1*** that are well-known. We also, as I said earlier, are doing studies that are called ***myeloid checkpoints essentially or myeloid immune suppressive cells.*** I am doing some studies with ***vaccines***, and I'm looking at ***other components of the immune system.***

Just to add one last detail: I'm actually doing a trial now where we're having patients ***exercise*** to see if that enhances their immune system.

Q. Interesting.

A. So in theory, that counts as immunotherapy.

Pernot Does Not Teach anti-PD-1 Therapies for MSI-H CRC



EX1006 (Pernot), 9

Table 1 Ongoing clinical trials, according to National Cancer Institute registration, using immunotherapy, according to strategy

Principle	Phase	Specificity	Registration number
(A) Peptide vaccine	I	Targeted peptide(s):	
		Ras mutated	NCT01322815
		MUC-1	NCT01556789
	I / II	HER2/neu	NCT01730118
		Survivin	NCT00108875
		Frame shift peptides (MSI)	NCT01461148
(B) Whole cell cancer vaccine	II	Nor-MDP	NCT01376505
		MUC-1	NCT01462513
	I / II	Characteristic of cancer cells:	
		Allogenic cancer cell	NCT00722228
(C) DC-based therapy	I / II	Autologous DCs intratumoral injection	NCT01882946
		Loaded with Frame shift antigens (MSI)	NCT01885702
		CEA-pulsed DCs' IL-2	NCT00154713
	II	Autologous DCs	NCT01348256
			NCT01413295
(D) Inhibition of immunoregulation	I / II	Immunomodulation strategy:	
		Treg depletion	NCT00986518
(E) Non specific immunostimulation	I / II	Anti-CTLA4 + local radiation therapy	NCT01769222
		Immunostimulatory agent	
		Recombinant vaccinia virus	NCT01394939
	II	IFN, Celecoxib + combination of chemokines	NCT01545141
		IL-7	NCT01339000
		Heat killed whole cell mycobacterium	NCT01539824
(F) Cell therapy	III	PGG beta-glucan: binding to neutrophils	NCT01309126
	II	Characteristic of cells	
		Allogenic activated lymphocytes	NCT00149006
			NCT00855452
	NS	Autologous TILS + lymphocyte depletion	NCT01174121
		Engineered autologous anti-ESO-1 lymphocytes	NCT00670748
		Engineered autologous anti-CEA lymphocytes	NCT01723306
		Autologous natural killer T cells	NCT01801852

Pernot Does Not Teach anti-PD-1 Therapies for MSI-H CRC



EX2163 (Neugut Dep.)
152:12–153:6

Q. Pernot does not disclose anti-PD-1 therapies; right?

A. No, correct.

Q. ***Pernot does not disclose that MSI high CRC patients would be promising candidates for PD-1 checkpoint blockade therapy; correct?***

A. ***No, he does not.***

Q. And ***Pernot does not disclose any relationship between MSI high CRC patients and their likelihood of responding to PD-1checkpoint blockade therapy; right?***

A. ***No***, he doesn't make reference to it.

Pernot Does *Not* Teach That CRC Patients Are Good Candidates

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021
Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. NILS LONBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/24 By: 
Nils Lonberg, Ph.D.

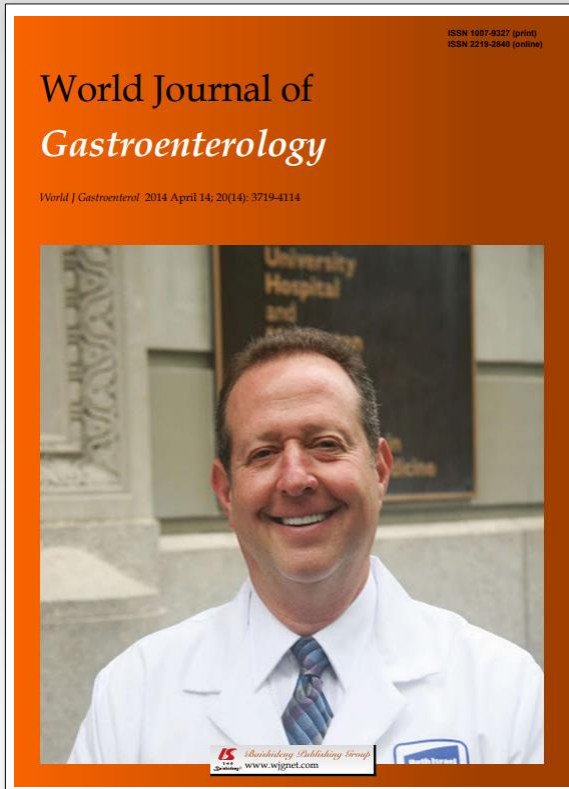
JHU 2072
Merck Sharp v. Johns Hopkins
IPR2024-00240

1

(Table 1, reproduced below).) And where Pernot *does* briefly mention anti-PD-1 therapies (*id.*, 6), it only does so in the context of melanoma—not MSI-H CRC or other MSI-H tumors. (*Id.*, 6 (“Recently some monoclonal antibodies targeting these molecules (PD1, CTLA-4) have shown more than promising efficacy results in solid neoplasia such as melanoma and others.”).) In my opinion, a POSA would not understand Pernot as disclosing or even suggesting that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy (or for pembrolizumab in particular).

EX2072 (Lonberg Decl.), ¶ 71

Pernot Does *Not* Teach That CRC Patients Are Good Candidates



EX1006 (Pernot), 2

Abstract

Strong evidence supports the concept of immunosurveillance and immunoediting in colorectal cancer. In particular, the density of T CD8⁺ and CD45⁺ lymphocyte infiltration was recently shown to have a better prognostic value than the classic tumor node metastasis classification factor. Other immune subsets, as macrophages, natural killer cells or unconventional lymphocytes, seem to play an important role. Induction of regulatory T cells (Tregs) or immunosuppressive molecules such as PD-1 or CTLA-4 and downregulation of antigen-presenting molecules are major escape mechanisms to antitumor immune response. The development of these mechanisms is a major obstacle to the establishment of an effective immune response, but also to the use of immunotherapy. Although im-

Merck's Other References Do Not Support RES

- Merck relies on other references but does not identify any specific disclosures to support RES
- Merck's other references provide only speculative statements that are insufficient to support a reasonable expectation of success
- Like with Pernot, Merck ignores portions of those references that teach away

Reply, 21; POR, 48–49; EX2072, ¶¶ 142–45 (discussing EX1032, e27817–5; EX1038, 9; EX1041, 9208; EX1042, 732; EX1051, e976052–6; EX1084, 1; EX1033, 2969)

Merck's Other References Teach Away From RES

Oncoimmunology 3, e27812, January 2014; © 2014 London Bioresearch

Exomics and immunogenetics

Bridging mutational load and immune checkpoints efficacy

Stéphane Champiat^{1,2}, Charles Ferte^{3,4}, Sophie Labat-Binec⁵, Alexandre Eggermont⁶, and Jean-Charles Soria^{1,2,4,6*}
¹Onc Development Department (DTPD) Gustave Roussy University Paris Saclay, Villejuif, France; ²Department of Medical Oncology Gustave Roussy University Paris Saclay, Villejuif, France; ³INSERM U981 Gustave Roussy University Paris Saclay, Villejuif, France; ⁴INSERM U981 Gustave Roussy University Paris Saclay, Villejuif, France; ⁵INSERM U981 Gustave Roussy University Paris Saclay, Villejuif, France; ⁶INSERM U981 Gustave Roussy University Paris Saclay, Villejuif, France

Abstract Anti-PD-1/PD-L1 antibodies are emerging as promising anticancer therapeutics. Interestingly, elevated response rates to these agents are mostly documented among patients with tumors that have high levels of somatic mutations, like melanoma or non-small cell lung carcinoma. We herein formulate the hypothesis that high levels of mutational heterogeneity in the tumor could be the key for the success of immune checkpoint-targeting therapies.

Keywords: immune checkpoints, immunotherapy, mutational heterogeneity, PD-1, PD-L1

Abbreviations: BRCA1, breast cancer 1, early onset; CTLA4, cytotoxic T lymphocyte-associated protein 4; IDO1, indoleamine 2,3-dioxygenase 1; IFN, interferon; IL, interleukin; MMR, mismatch repair; MSI, microsatellite instability; NSCLC, non-small cell lung carcinoma; ORR, overall response rate; PD-L1, programmed cell death 1; PD-L1, PD-1 ligand 1; RCC, renal cell carcinoma; TGFβ, transforming growth factor β; TKI, tyrosine kinase inhibitor

*Correspondence to: Stéphane Champiat, trial chemotherapy
 Submitted: 12/09/2013
 Revised: 01/10/2014
 Accepted: 01/10/2014
 Published Online: 01/10/2014

Charles Ferte, Sophie Labat-Binec, Alexandre Eggermont, Jean-Charles Soria, and Stéphane Champiat
 Bridging mutational load and immune checkpoints efficacy
 Oncoimmunology 2014; 3:e27812
 http://dx.doi.org/10.4049/oi.2013.007

www.londonbioresearch.com

Oncoimmunology

427812.1
 MERCK EX1032

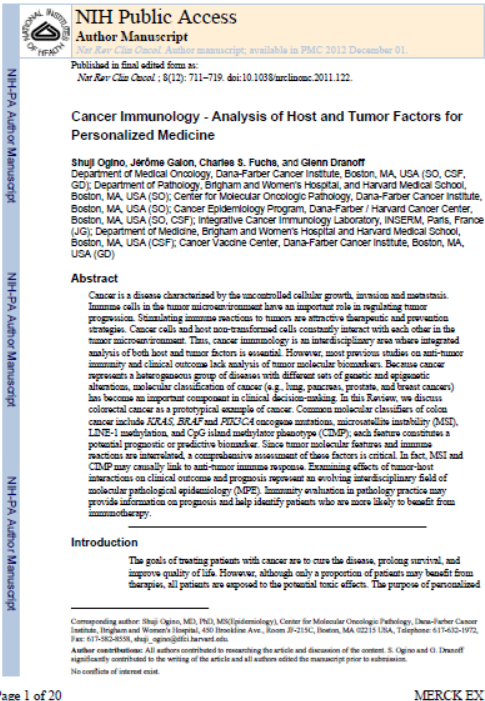
Page 1 of 6

EX1032 (Champiat), Table 1

Table 1. PD-1 and PD-L1 overall response rates across solid tumors

		ORR				
		anti-PD1 agent		anti-PD-L1 agent		
	mutation rate median frequency of somatic mutations per Mb	Nivolumab BMS-936558	Lambrolizumab MK 34-75	BMS-936559 MDX-1105 MEDI 4736	MPDL 3280 A	PD-L1 expression
Melanoma	13,2	28% (26/94)	38% (44/117)	17% (9/52)	29% (11/38)	40–100 %
NSCLC former/ current smoker	10,5				26% (11/43)	
NSCLC squamous	8,17	33% (6/18)		8% (1/13)	27% (3/11)	35–95 %
NSCLC non squamous	6,43	12% (7/56)		11% (4/36)	21% (9/42)	35–95 %
Colorectal	3,2	0% (0/19)		0% (0/18)		53%
Ovarian	1,65			6% (1/17)		33–80 %
Renal Cell Carcinoma	1,53	27% (9/33)		12% (2/17)	13% (6/47)	15–24 %
Prostate	0,73	0% (0/13)				
NSCLC never smoker	0,6				10% (1/10)	
References	Lawrence et al. 2013 Govindan et al. 2012	Topalian et al. 2012	Hamid et al. 2013	Brahmer et al. 2012	Hamid et al. 2013 Soria et al. 2013 Cho et al. 2013	Chen et al. 2012

Merck's Other References Teach Away From RES



EX1035 (Ogino), 2

treatment benefit and minimize adverse effects. To achieve this goal, informative biomarkers need to be identified to stratify patients for specific therapies. As tumors are heterogeneous and show distinctive genetic and epigenetic profiles, there may not be a single biomarker that will prove sufficient information for predicting treatment response and patient outcome. Examples of informative tumor biomarkers are molecular features of neoplastic cells, including *EGFR* mutations in lung cancer;^{1,2} microsatellite instability (MSI) in colorectal cancer;³⁻⁵ *ESR1* (ER- α), *PGR* and *ERBB2* (HER2) expression in breast cancer;^{6,7} *TMPRSS2-ERG* translocation in prostate cancer;⁸ and CpG island methylation, and *KRAS*, *BRAF*, *PIK3CA* and *TP53* mutations in multiple cancer types.⁹⁻¹¹

BMS Nivolumab Study Does Not Support RES

- Only one out of 33 CRC patients responded to treatment with nivolumab
 - EX1002, 205; EX1057, 2–3; EX2176, 22; EX2072, ¶ 166; EX2090, ¶ 52
- “Statistically meaningless”
 - EX1002, 205 (Pardoll Dec.)



Cancer treatment has a 97% failure rate



The only reasonable expectation is ***“failure, not success”***

OSI Pharms., 939 F.3d at 1385

Pet., 44; EX1057

BMS Investigators Suspected PD-L1, Not MSI-H

Published OnlineFirst November 20, 2012; DOI: 10.1158/1078-0432.CCR-12-2625

Cancer Therapy: Clinical

Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody

Evan J. Lipson¹, William H. Sharfman^{1,3}, Charles G. Drake^{1,2}, Ira Wollner⁶, Janis M. Taube^{3,4}, Robert A. Anders⁴, Haiying Xu⁴, Sheng Yao^{1,3}, Alice Pons¹, Lieping Chen^{1,3}, Drew M. Pardoll¹, Julie R. Brahmer¹, and Suzanne L. Topalian⁵

Abstract

Purpose: Results from the first-in-human trial of the anti-programmed death-1 (PD-1) antibody BMS-936558 in patients with treatment-refractory solid tumors, including safety, tolerability, pharmacokinetics, and immunologic correlates, have been previously reported. Here, we provide long-term follow-up on those patients from that trial who sustained objective tumor regressions off therapy, and test the hypothesis that reinduction therapy for late tumor recurrence can be effective.

Experimental Design: These patients with colorectal cancer, renal cell cancer, and melanoma achieved objective responses on an intermittent dosing regimen of BMS-936558. Following cessation of therapy, patients were followed for more than 3 years. A patient with melanoma who experienced a prolonged partial response followed by tumor recurrence received reinduction therapy.

Results: A patient with melanoma experienced a complete response, which recurred after 3 years. A patient with renal cell cancer experienced a partial response lasting 3 years off therapy, which recurred to a complete response, which is ongoing at 12 months. A patient with melanoma achieved a partial response that was stable for 16 months off therapy; recurrent disease was successfully treated with reinduction anti-PD-1 therapy.

Conclusion: These data represent the most prolonged observation to date of patients with solid tumors responding to anti-PD-1 immunotherapy and the first report of successful reinduction therapy following delayed tumor progression. They underscore the potential for immune checkpoint blockade with anti-PD-1 to meet the equilibrium between tumor and the host immune system. *Clin Cancer Res* 19(21):4023-4. ©2012 AACR.

Introduction

The specific or selective expression of antigens by cancer cells creates an opportunity for endogenous cell-mediated and adaptive immune attack and for immunotherapeutic interventions. The development of effective cancer immunotherapies depends on reversing inhibitory and co-inhibitory signals in the tumor microenvironment, thereby enhancing the visibility of tumor cells to the immune system. In the last decade, it has become clear that the

immune regulatory pathway composed of programmed death-1 (PD-1, CD279), a receptor expressed on activated T cells, and its ligands PD-L1 (B7-1, CD274) and PD-L2 (B7-2, CD275), plays an integral role in the downregulation of antitumor immunity. Inhibition of this pathway using blocking monoclonal antibodies (mAb) against PD-1 or PD-L1 is emerging as an effective method for reversing cancer immune suppression and thereby restoring antitumor responses in patients with advanced disease (1). Although such therapies are still in development, they have shown promising clinical results not only for tumors classically considered to be immunogenic such as melanoma and renal cell carcinoma (RCC), but also for common epithelial malignancies such as non-small cell lung cancer (NSCLC), breast cancer, and colorectal cancer (CRC).

BMS-936558 (MPD-31-02) is a blocking mAb specific for human PD-1. The first-in-human single-dose, dose-escalation trial of this agent reported by Brahmer and colleagues (2) enrolled 39 patients with treatment-refractory metastatic solid tumors including melanoma, RCC, colorectal cancer (CRC), NSCLC, and castration-resistant prostate cancer (CRPC). A favorable safety profile and preliminary evidence of clinical activity in all histologies except CRPC led to the design of a multicourse trial of

Cancer Therapy: Clinical

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Durable complete response in colorectal cancer

A 71-year-old male with CRC underwent a right hemicolectomy in October 2003, revealing a moderately differentiated adenocarcinoma with metastases to 4 of 16 pericolic lymph nodes and vascular and perineural invasion [G₂, pT3N2; **microsatellite instability (MSI)-high genotype**]. He received adjuvant 5-fluorouracil (5-FU) and

and CD3+ T cells (Fig. 1B). We have previously reported preliminary evidence for a **correlation between tumor cell membranous PD-L1 expression and the likelihood of response to anti-PD-1 therapy** (2). Potential relationships between **PD-L1 expression** on nontumor cells and clinical outcomes **require further study** (4).

EX1057, 2–3

Merck's Study on Keytruda® and PD-L1 CRC Failed

RESEARCH ARTICLE

Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma

Published: December 28, 2017

Results

Of 137 patients with CRC and samples evaluable for PD-L1 expression, 33 (24%) had PD-L1-positive tumors, of which 23 were enrolled. Median follow-up was 5.3 months, and 8 patients (35%) reported treatment-related adverse events (AEs), most commonly fatigue (n = 3, 13%), stomatitis (n = 2, 9%), and asthenia (n = 2, 9%). One patient (4%) experienced grade 4 treatment-related increased blood bilirubin. No grade 3 AEs, discontinuations, or deaths were attributed to treatment. Most patients (n = 15, 65%) experienced progressive disease. One partial response occurred in a patient (4%) with MSI-high CRC.

Conclusion

Pembrolizumab demonstrated a favorable safety profile in advanced PD-L1-positive CRC. Antitumor activity was observed in a single patient with MSI-high CRC, warranting further evaluation in this patient population. (Clinicaltrials.gov registration: NCT02054806)

PLOS ONE

RESEARCH ARTICLE

Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma

Bart H. Orlowski¹, John M. Wainwright², David L. Lenz³, Elena Blas⁴, Judith Rabinovich⁵, Carlos Gomez-Roca⁶, Samuel Egger⁷, Sergio A. Khan-Pou⁸, Mark N. Bates⁹, Abhinav R. Abdul Razak¹⁰, Kasia Dusz¹¹, Amanda Santoro¹², Roger B. Cohen¹³, Mariana Gould¹⁴, Sander Staud¹⁵, Nanni Betti¹⁶, Sue-Wen Han¹⁷

1 Department of Hematology/Oncology, Indiana University Simon Cancer Center, Indianapolis, Indiana, United States of America, **2** Department of Hematology/Oncology, Maryland Hematology/Oncology, Rockville, Maryland, United States of America, **3** Houston Cancer Targeted Therapy Group, The Royal Marsden, Sutton, United Kingdom, **4** Val d'Auvergne Hematology/Oncology, Val d'Auvergne University Hospital, Clermont-Ferrand, France, **5** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **6** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **7** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **8** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **9** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **10** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **11** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **12** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **13** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **14** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **15** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **16** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain, **17** Department of Hematology/Oncology, Institut de Ciències del Càncer, Barcelona, Spain

OPEN ACCESS
Citation: Orlowski BH, Wainwright JM, Lenz D, Blas E, Rabinovich J, Gomez-Roca C, et al. (2017) Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. PLoS ONE 12(12): e0189444. doi:10.1371/journal.pone.0189444

Abstract
Colorectal cancers (CRCs) expressing programmed death ligand 1 (PD-L1) have poor prognosis. In the multicohort KEYNOTE-028 trial, the anti-PD-1 antibody pembrolizumab was evaluated in 20 PD-L1-positive advanced solid tumors. Herein, we report results for the advanced CRC cohort.

Background
Colorectal cancers (CRCs) expressing programmed death ligand 1 (PD-L1) have poor prognosis. In the multicohort KEYNOTE-028 trial, the anti-PD-1 antibody pembrolizumab was evaluated in 20 PD-L1-positive advanced solid tumors. Herein, we report results for the advanced CRC cohort.

Methods
Patients with advanced, treatment-resistant PD-L1-positive carcinoma of the colon or rectum were enrolled, regardless of metastatic to distant (M1) status. Pembrolizumab 10 mg/kg was administered every 2 weeks for up to 2 years or until disease progression/unacceptable toxicity. Response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. Primary end points were safety and overall response rate by investigator review per Response Evaluation Criteria in Solid Tumors version 1.1. Data cutoff was June 20, 2016.

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No Results from BMS MSI-H CRC Trial As of Critical Date



EX2404 (Oberstein Dep.),
286:25–287:16

Q. As of July 10, 2015, were results available for the BMS clinical trial testing MSI-high colorectal cancer that you mentioned?

A. There were no results that I know of that were available. As you mentioned BMS, there were, of course, results from a prior single patient where MSI-high colon cancer was treated with nivolumab, which was a drug made by BMS, and a person of ordinary skill would have known the public information that that patient had a complete response after treatment with PD-1 antibody.

Q. But that was a single patient; correct?

A. That was a single patient with MSI-high colorectal cancer.

Merck's Remaining Evidence Does Not Support RES

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

IPR2024-00240
Patent No. 11,591,393

PETITIONER'S REPLY

Reply 21–22

- Dr. Lonberg's ***own*** "enthusiasm"
- Dr. Goldberg's testimony that companies were "aggressively researching ***immune-oncology opportunities***"
- Dr. Lonberg's agreement that documents 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; EX1136, 80:13–82:13

Motivation to Pursue Does Not Show RES



It is “***not enough*** for the appellant-defendant to have shown that a skilled artisan ***would have pursued*** the claimed method as a treatment option, but the appellant-defendant also had to show that the skilled artisan would have reasonably expected to achieve success in the treatment.”

Eli Lilly & Co. v. Teva Pharms. Int’l GmbH, 8 F.4th 1331, 1344 (Fed. Cir. 2021)



Overwhelming Objective Indicia of Non-Obviousness

This Is A Unique Case

- JHU is an academic institution
 - Conceived and reduced to practice a novel method for treating MSI-H CRC using pembrolizumab
 - Designed and conducted clinical trial to test hypothesis
- Merck is a pharmaceutical company
 - Markets and sells pembrolizumab under the brand name Keytruda®
 - Keytruda® label has FDA-approved indications ***specifically*** for treating CRC patients determined to have MSI-H tumors

POR, 58

Objective Indicia Require Nexus With Claimed Invention

- Patent Owner has the burden of showing nexus
 - **Presumption** “when the asserted objective evidence is tied to a specific product and that product **is** the invention disclosed and claimed in the patent.” *WBIP*, 829 F.3d at 1329 (“coextensiveness”)
 - Even if no presumption, Patent Owner can prove nexus “by showing that the evidence of secondary considerations is the direct result of the unique characteristics of the claimed invention.” *Fox Factory*, 944 F.3d at 1373
- Patent challenger has the burden to rebut presumed nexus
 - By presenting **evidence** that shows the proffered objective evidence was due to extraneous factors other than the patented invention (e.g., additional unclaimed features, improvements in marketing, superior workmanship)

POR, 59–67

Presumption of Nexus



There is a presumption of nexus when a “product embodies the invention and is coextensive with it.”

Volvo Penta of the Americas, LLC v. Brunswick Corp.,
81 F.4th 1202, 1211 (Fed. Cir. 2023)

POR, 59

JHU Met Its Burden For Presumption of Nexus

- Every step of the claimed treatment method is set forth in Merck's Keytruda® label for indications
 - “1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer”
 - “1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer”

POR, 60; EX2129, 5; EX2177; EX2179

CRC Indications Embody Claimed Invention & Coextensive

1[pre]. A method of treating [MSI-H/dMMR CRC] in a human patient, the method comprising:

1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response [see *Clinical Studies (14.8)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

POR, 60–61; EX2129, 5

CRC Indications Embody Claimed Invention & Coextensive

1[a]. testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is [MSI-H/dMMR]; and

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, or TMB-H Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation [see *Clinical Studies (14.2)*].
- metastatic NSCLC [see *Clinical Studies (14.2)*].
- first-line treatment of metastatic or unresectable, recurrent HNSCC [see *Clinical Studies (14.4)*].
- metastatic urothelial carcinoma [see *Clinical Studies (14.7)*].
- metastatic gastric cancer [see *Clinical Studies (14.10)*]. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- metastatic esophageal cancer [see *Clinical Studies (14.11)*].
- recurrent or metastatic cervical cancer [see *Clinical Studies (14.12)*].

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens [see *Clinical Studies (14.8, 14.9)*].

CRC Indications Embody Claimed Invention & Coextensive

1[a]. testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is [MSI-H/dMMR]; and

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

POR, 62; EX2129, 73–75

CRC Indications Embody Claimed Invention & Coextensive

1[b]. in response to determining that the [CRC is MSI H/dMMR], treating the patient with a therapeutically effective amount of pembrolizumab.

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months
* 30-minute intravenous infusion		

CRC Indications Embody Claimed Invention & Coextensive

1[b]. in response to determining that the [CRC is MSI H/dMMR], treating the patient with a therapeutically effective amount of pembrolizumab.

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

Table 51: Response by Tumor Type

	N	Objective Response Rate		Duration of Response range (months)
		n (%)	95% CI	
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)

CRC Indications Embody Claimed Invention & Coextensive

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Table 52: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
Objective Response Rate‡		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Duration of Response§		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 months¶	75%	37%
% with duration ≥24 months¶	43%	18%

* Based on Cox regression model

† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)

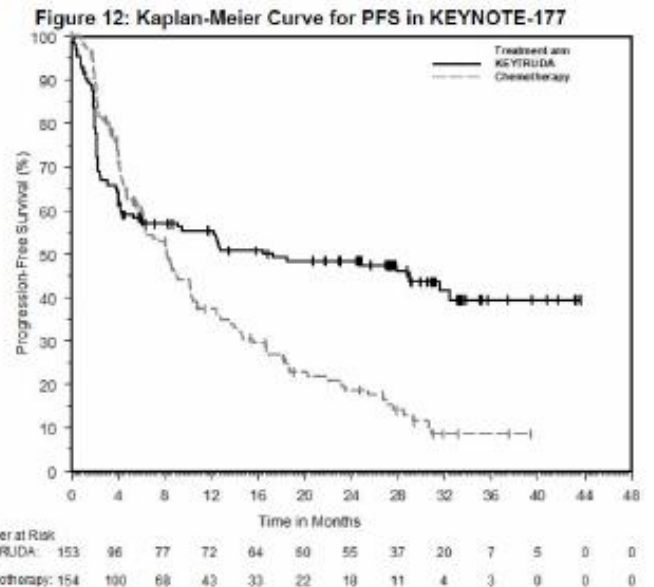
‡ Based on confirmed response by BICR review

§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm

¶ Based on observed duration of response

+ Denotes ongoing response

NR = not reached



POR, 63; EX2129, 73–75

Merck Fails to Rebut Nexus Presumption with Evidence



Merck cannot rebut the presumption of nexus “with argument alone—it must present **evidence.**”

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1329 (Fed. Cir. 2016)

Patent challenger must “**adduce evidence**” showing objective indicia “due to extraneous factors other than the patented invention ... argument and conjecture are insufficient.”

Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1393 (Fed. Cir. 1988) (cleaned up)

POR, 65

Merck Presents No Evidence, Only Attorney Argument

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner

v.

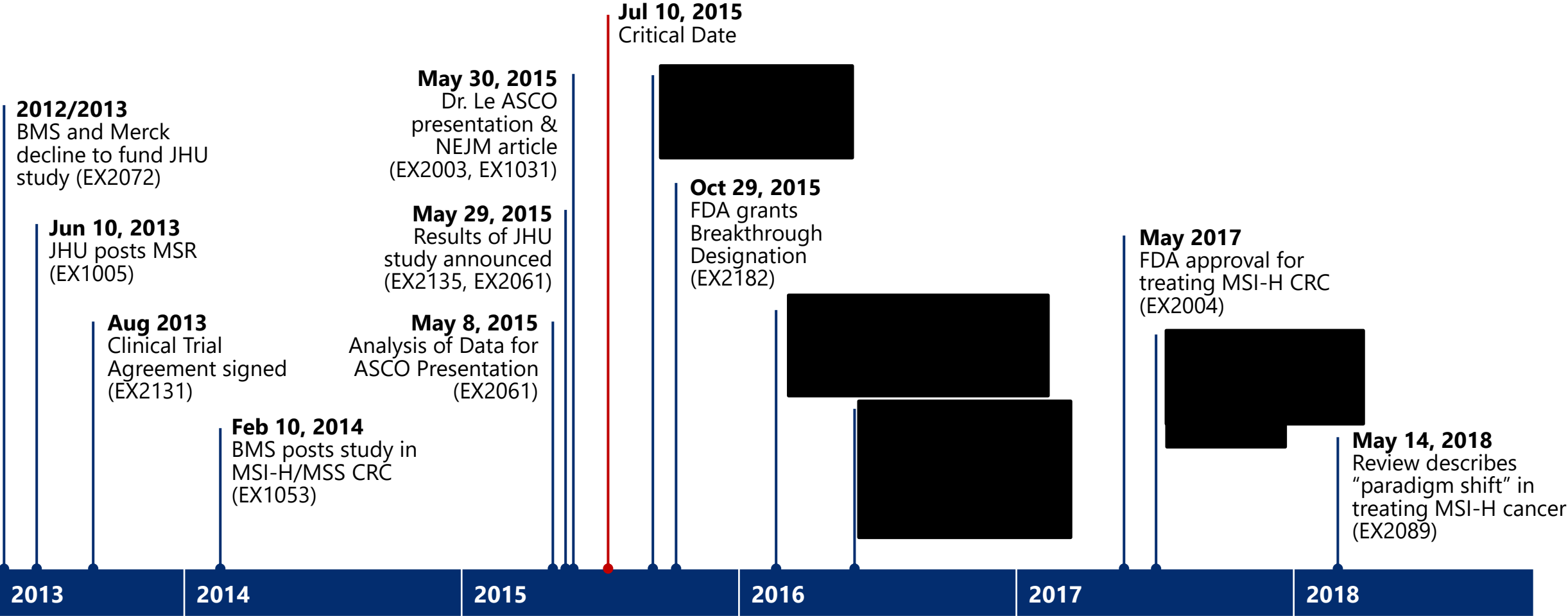
JHU and its declarants fail to meet the burden of establishing nexus for any alleged secondary considerations. There can be no nexus when the claimed feature was “indisputably known in the prior art.” *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017); see also *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (“Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.”) (citation omitted).

Reply, 23–33

- Claimed method was ***not*** “indisputably known in the prior art”
- Dr. Oberstein offers no opinion on nexus
 - EX2404, 240:14–241:22
- Dr. Sheridan presumes that there is no nexus because of alleged anticipation
 - EX1151, ¶¶ 40–42

Sur-Reply, 19–20

Timeline of Objective Indicia Evidence



Timeline of Objective Indicia Evidence

Objective Indicia Show '393 Patent Non-Obvious

	Long-Felt Need
	Unexpected Results
	Commercial success
	Industry Praise
	Skepticism

Dr. Goldberg: Long-Felt, Unmet Need for MSI-H CRC Patients

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021
Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. RICHARD GOLDBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: October 4, 2024 By: Richard Goldberg, M.D.

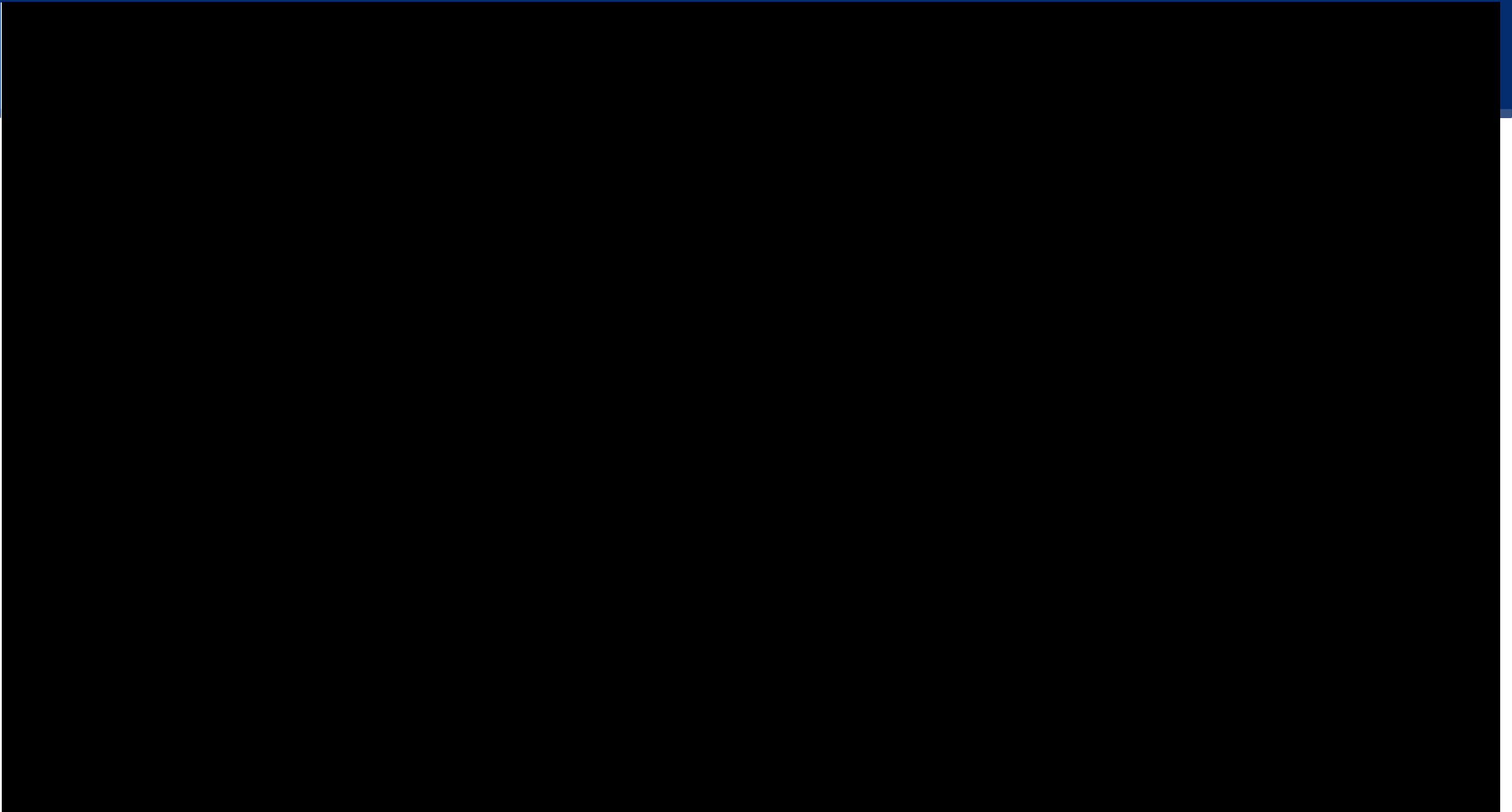
JHU 2090
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IPR2024-00240

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65. Circumstances like this when patients with very advanced disease can have their future so dramatically altered from incurable to cured are almost unheard of, and this is the only such treatment I have encountered in my 35 years of practicing oncology. They, their families, and we as their caregivers sometimes get to participate in miracles, and that is what this discovery felt like at the time. Without JHU's invention, MSI-H CRC patients would have faced a limited set of treatment options that would have quickly run out. JHU's invention met this long-felt need for treating and in many cases curing MSI-H CRC cancers that would have previously been a death sentence for those patients.

EX2090 (Goldberg Decl.), ¶ 65

POR, 76–78



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Merck Experts Affirm Long-Felt, Unmet Need



EX2163 (Neugut Dep.),
181:15–25

Q. I appreciate that you cure people using Keytruda, the MSI high CRC patients.

Before you had Keytruda, were you curing MSI high CRC patients?

A. ***Curing a patient with a metastatic solid tumor, it's a very rare phenomenon.*** I would say in my career, which stretches back 40 years and encompasses thousands of patients, I've cured seven. And with ***Keytruda and MSI high colon cancer, I've probably cured another seven in the last five years.***

POR, 77

Objective Indicia Show '393 Patent Non-Obvious

✓	Long-Felt Need
✓	Unexpected Results
	Commercial success
	Industry Praise
	Skepticism

JHU's Clinical Trial Results Were Unexpected

	MMR-deficient ¹⁸ CRC (n = 10)	MMR-proficient CRC (n = 18)	MMR-deficient non-CRC (n = 7)
Complete Response (%)	0 (0)	0 (0)	1 (14)
Partial Response (%)	4 (40)	0 (0)	4 (57)
Stable Disease (Week 12) (%)	5 (50)	2 (11)	0 (0)
Progressive Disease (%)	1 (10)	11 (61)	2 (29)
Not Evaluable (%)	0 (0)	5 (28)	0 (0)
Immune-related objective response rate (irORR) (95% CI)	40 (12-74)	0 (0-19)	71 (29-96)
Immune-related disease control rate (95% CI)	90 (55-100)	11 (1-35)	71 (29-96)
Immune-related PFS at 20 weeks (95% CI)	78 (40-97)	11 (1-35)	67 (22-96)

- Before: Studies testing pembrolizumab or other PD-1 inhibitors in CRC patients had **97% and 95% failure rates**
- After: **90%** of MMR-deficient CRC patients showed either a partial response or stable disease at week 12, while only 11% of MMR-proficient CRC patients had stable disease at week 12; the rest of the patients' tumors had progressed
- Five-year overall survival rate of **57.5%**, meaning over half of the patients were still alive five years after their initial treatment.

POR, 81; Sur-Reply, 20-21; EX1001, Fig. 11 (cleaned up); EX2090, ¶ 41

Inventors Were Hopeful But Extraordinary Results Not Anticipated



EX2121, 6

At first, Drew Pardoll, director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy and co-director of the Cancer Immunology Program at Hopkins, told Diaz that checkpoint inhibitors didn't seem to be working in colorectal cancer.

However, later, a good, strong response showed up.

"I said, 'Check it for MSI-high,' and it was MSI-high," Diaz said.

"We get the drug from Merck, we write the protocol, and we start enrolling patients, and these patients are doing miraculously well. The tumors are melting away," Diaz said. "These were people who were treatment-refractory. One was hospice-bound.

"Things don't work a lot. When something works, it's unbelievable!"

POR, 66

Inventors Were Hopeful But Extraordinary Results Not Anticipated

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021
Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. DUNG LE

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/2024 By: Dung Le Digitally signed by Dung Le
Dung Le, M.D. Date: 2024.10.04 11:39:22 -0500

JHU 2130
Merck Sharp & Johns Hopkins
IPR2024-00240

EX2130, ¶¶ 30–31

30. These outcomes were extraordinary and to my knowledge had not been seen previously in a clinical trial of a cancer drug. For comparison, other therapies for CRC in clinical trials at this time were showing response rates on the order of 1%. EX2113 (Grothey CORRECT Trial Lancet 2013).

31. Importantly, the patients in our study had failed on prior cancer therapies and were often in hospice care or otherwise close to the end of their lives. To see these patients respond so dramatically was indeed miraculous. To that point in my career as a cancer researcher and physician treating cancer patients, I had not seen such remarkable responses to any treatment. This was an incredibly rewarding time for me as a doctor. For our study patients who came to us with bleak prognoses, the results were miraculous. In many cases, these patients are living normal, cancer-free lives.

POR, 81

If Results Obvious, Trial Would Have Been Unethical

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
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Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

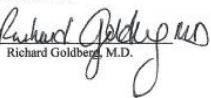
DECLARATION OF DR. RICHARD GOLDBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

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Dated: October 4, 2024

By:


Richard Goldberg, M.D.

JHU 2090
Merck Sharp v. Johns Hopkins
IPR2024-00240

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EX2090 (Goldberg Decl.), ¶ 60

60. It should be noted that these studies were all approved by institutional review boards at the institutions where patients were enrolled. Institutional review boards are specifically tasked with determining if the proposed clinical trial is ethical in its treatment of patients. JHU's study could not have moved forward without approval by the IRB. Had the results of the trial been obvious before it was conducted, *i.e.* that it was obvious that the MSS cohort would not respond, it would have been unethical to construct such a protocol, let alone enroll patients to cohort B, and the IRB would not have approved the trial.⁴⁰ While those patients did not have MSI-H tumors and the results of the study showed that group did not respond to pembrolizumab, those results were not predictable or known prior to conducting the trial.

POR, 66

Degree of Success Is Relevant to Unexpected Results



“Unexpected results are 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)

Sur-Reply, 21–22

Objective Indicia Show '393 Patent Non-Obvious

	Long-Felt Need
	Unexpected Results
	Industry Praise
	Commercial success
	Skepticism

JHU Results Greeted with Fanfare at 2015 ASCO Meeting

ASCO 2015: Mismatch Repair Deficiency Predicts Response to Pembrolizumab Among Patients With Colorectal and Other Cancers

ASCO 2015: Mismatch Repair Deficiency Predicts Response to Pembrolizumab Among Patients With Colorectal and Other Cancers

By The ASCO Post
Posted: 5/29/2015 4:32:10 PM
Last updated: 5/29/2015 4:32:10 PM

Key Points

- Mismatch repair deficiency predicted response to the anti-PD-1 antibody pembrolizumab among patients with advanced colorectal, endometrial, and several types of gastrointestinal cancers.
- Responses occurred in 62% of patients with mismatch repair–deficient colorectal cancers but none of the patients with mismatch repair–proficient tumors.
- Disease control rates were 92% among patients with mismatch repair–deficient colorectal cancers and 16% in the mismatch repair–proficient group.
- An overall response rate of 60% was observed in patients with other mismatch repair–deficient cancers.

A phase II study identified the first genomic marker—mismatch repair deficiency—to predict clinical benefit of immune checkpoint blockade with the anti-PD-1 antibody pembrolizumab (Keytruda). Among 50 patients with colorectal cancer, 62% of the 25 patients with mismatch repair–deficient tumors responded to pembrolizumab, but no responses were seen among the 25 mismatch repair–proficient patients. The difference in disease control rates (responses plus stable disease) was even greater: 92% in the mismatch repair–deficient group and only 16% in the mismatch repair–proficient group.

An overall response rate of 60% was observed in patients with mismatch repair–deficient advanced endometrial cancer and several types of advanced gastrointestinal cancers including ampullary, duodenal, cholangiocarcinoma, and gastric cancers. “The responses were durable in a treatment-refractory patient population, and many of these responses are ongoing for over a year,” the study’s lead author, **Dung T. Le, MD**,

Assistant Professor of Oncology at Johns Hopkins Kimmel Cancer Center in Baltimore, stated at a press conference at the 2015 ASCO Annual Meeting in Chicago. The full study will be presented at the clinical science symposium on immunotherapy on Saturday, May 30 (Abstract LBA100).

JHU 2135
Merck Sharp & Dohme v. Johns Hopkins
IPR2024-00240

- Disease control rates were 92% among patients with mismatch repair–deficient colorectal cancers and 16% in the mismatch repair–proficient group.
- An overall response rate of 60% was observed in patients with other mismatch repair–deficient cancers.

An overall response rate of 60% was observed in patients with mismatch repair–deficient advanced endometrial cancer and several types of advanced gastrointestinal cancers including ampullary, duodenal, cholangiocarcinoma, and gastric cancers. “The responses were durable in a treatment-refractory patient population, and many of these responses are ongoing for over a year,” the study’s lead author, **Dung T. Le, MD**,

Assistant Professor of Oncology at Johns Hopkins Kimmel Cancer Center in Baltimore, stated at a press conference at the 2015 ASCO Annual Meeting in Chicago. The full study will be presented at the clinical science symposium on immunotherapy on Saturday, May 30 (Abstract LBA100).

EX2135, 1

POR, 68–71; Sur-Reply, 26

ASCO Is Super Bowl of the Cancer World

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

Patent No. 11,591,393

DECLARATION OF ALFRED I. NEUGUT, M.D., Ph.D., M.P.H.

¹ Merck and JHU authors also publicly shared more about the MSI-H Trial when they published an abstract about the study and presented a poster about it on June 1, 2014 at the American Society of Clinical Oncology (“ASCO”), an oncology convention. (EX1079; EX1080.) ASCO is an annual meeting for oncologists, which is considered the super bowl of the cancer world, and attended by over 40 thousand oncologists and others each year. Until 2020, I regularly attended ASCO.

EX1003 (Neugut Decl.),
¶ 35, FN1

POR, 68–69

JHU's Results Published in *New England Journal of Medicine*

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Lubner, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zahner, C.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhajee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

ABSTRACT

BACKGROUND Somatic mutations have the potential to encode “non-self” immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

METHODS We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti-programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days in patients with mismatch repair–deficient colorectal cancers, patients with mismatch repair–proficient colorectal cancers, and patients with mismatch repair–deficient cancers that were not colorectal. The coprimary end points were the immune-related objective response rate and the 20-week immune-related progression-free survival rate.

RESULTS The immune-related objective response rate and immune-related progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair–deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair–proficient colorectal cancers. The median progression-free survival and overall survival were not reached in the cohort with mismatch repair–deficient colorectal cancer but were 2.2 and 5.0 months, respectively, in the cohort with mismatch repair–proficient colorectal cancer (hazard ratio for disease progression or death, 0.10 [$P<0.001$], and hazard ratio for death, 0.22 [$P=0.05$]). Patients with mismatch repair–deficient noncolorectal cancer had responses similar to those of patients with mismatch repair–deficient colorectal cancer (immune-related objective response rate, 77% [5 of 7 patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]). Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in mismatch repair–deficient tumors, as compared with 73 in mismatch repair–proficient tumors ($P=0.007$), and high somatic mutation loads were associated with prolonged progression-free survival ($P=0.02$).

CONCLUSIONS This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others; ClinicalTrials.gov number, NCT01876511.)

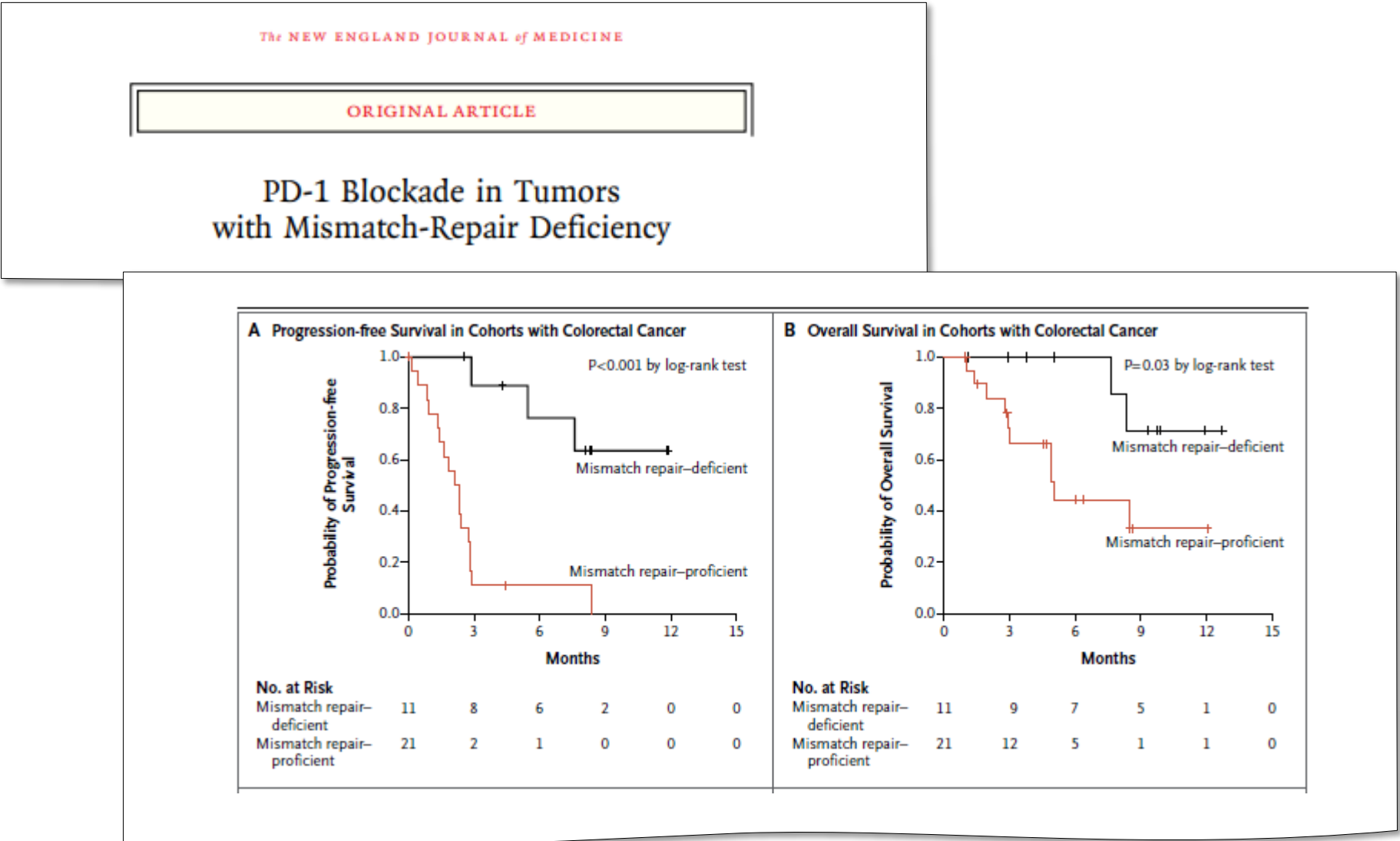
THE NEW ENGLAND JOURNAL OF MEDICINE

This article was published on May 30, 2015, at NEJM.org.

N Engl J Med 2015;372:2509–20. DOI: 10.1056/NEJMoa1500596 Copyright © 2015 Massachusetts Medical Society

2509

EX1031, 1, 7



POR, 69–70

JHU's Results Published in *New England Journal of Medicine*



EX2163 (Neugut Dep.),
109:12–19, 109:24–110:4

- Q. Why do you get the New England Journal of Medicine?
- A. Well, they send it to me for free, and it is sort of the leading -- the most -- it has I guess the most -- I don't want to say the most important, but certainly the most -- well, I guess ***the most prominent papers that are published in medicine.***
- ***
- Q. What's your view of the reputation of the New England Journal of Medicine?
- A. I mean, as I said, ***it's considered the most prestigious journal.***

Merck Publicly Praised JHU's "Exciting" Results



NEWS RELEASE

First Study Evaluating DNA Mismatch Repair as Genetic Guide for Immunotherapy Treatment with Merck's KEYTRUDA® (pembrolizumab) Presented at 2015 ASCO Annual Meeting and Published in the New England Journal of Medicine

5/29/2015

Early Findings Show DNA Mismatch Repair-Deficient Colorectal and Other Tumors Highly Responsive to Checkpoint Blockade with Anti-PD-1 Therapy

Merck Plans to Initiate Phase 2 Registrational Study with KEYTRUDA (KEYNOTE-164) to Evaluate MMR Deficiency in Colorectal Cancer

KENILWORTH, NJ.-(BUSINESS WIRE)-Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced results from the first study evaluating the correlation of benefit with an immunotherapy based on DNA mismatch repair (MMR) deficiency, a well-established form of genetic instability in many cancers characterized by the loss of function of the MMR pathway. The Phase 2 study, led by researchers from Johns Hopkins Kimmel Cancer Center, evaluated Merck's anti-PD-1 therapy, KEYTRUDA® (pembrolizumab), in 48 evaluable, heavily pre-treated patients with advanced colorectal cancer and other solid tumors. In the colorectal cancer group with MMR-deficient tumors, an objective response rate (ORR) of 62 percent was observed (n=8/13). In contrast, no responses were observed in the colorectal cancer group with MMR-proficient tumors (n=0/25). At the time of analysis, the median progression-free survival (PFS) and overall survival (OS) were not reached in the MMR-deficient colorectal cancer group. These data, featured today in the American Society of Clinical Oncology (ASCO) Press Program and published in the New England Journal of Medicine, will be presented in an oral session by Dr. Dung Le on Saturday,

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IPR2024-00240

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EX2061, 2

NEWS RELEASE

First Study Evaluating DNA Mismatch Repair as Genetic Guide for Immunotherapy Treatment with Merck's KEYTRUDA® (pembrolizumab) Presented at 2015 ASCO Annual Meeting and Published in the New England Journal of Medicine

5/29/2015

Early Findings Show DNA Mismatch Repair-Deficient Colorectal and Other Tumors Highly Responsive to Checkpoint Blockade with Anti-PD-1 Therapy

"These exciting results, while early, suggest that evidence of DNA mismatch repair deficiency may be an important way of identifying tumors that are responsive to checkpoint blockade," said Dr. Roger Dansey, therapeutic area

head and senior vice president, oncology late-stage development, Merck Research Laboratories. "DNA mismatch repair deficiency is an established biomarker in many types of cancer and these results open the door for research with KEYTRUDA in colorectal cancer and other tumor types with this potentially clinically meaningful tool. We look forward to initiating a registrational Phase 2 study of KEYTRUDA in patients with colorectal cancer to further explore this genomic biomarker."

POR, 72-73; EX2060, 2

Post-FDA Approval, Merck Publicly Praised JHU's Invention



Menu

Media > News releases > News release

FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors

"The FDA's approval of this first-of-its-kind, tumor-agnostic, indication is further evidence of Merck's commitment to helping people with difficult-to-treat cancers, and to advancing the use of biomarkers to guide clinical decision-making," said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. "This is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and clinicians at Johns Hopkins University for their important scientific work, as well as the patients and their families who helped make today's approval possible."



Menu

Media > News releases > News release

FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors

Print

May 25, 2017 6:00 pm ET

KEYTRUDA Now Approved for MSI-H or dMMR Patients Whose Disease Has Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes Patients with Colorectal Cancer That Has Progressed Following Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan

With this Unique Indication, KEYTRUDA is the First Cancer Therapy Approved for Use Based on a Biomarker, Regardless of Tumor Type

KENILWORTH, N.J. – Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA® (pembrolizumab), the company's anti-PD-1 (programmed death receptor-1) therapy, for a first-of-its-kind indication: the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient, solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under the FDA's accelerated approval regulations based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

Immune-mediated adverse reactions occurred with KEYTRUDA including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate.

JHU 2060
Merck Sharp & Dohme
IPR2024-00240

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EX2060, 2

POR, 72–73

FDA Publicly Praised JHU's Invention

FDA NEWS RELEASE

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release:
May 23, 2017

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

"This is an important first for the cancer community," said Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location."

MSI-H and dMMR tumors contain abnormalities that affect the proper repair of DNA inside the cell. Tumors with these biomarkers are most commonly found in colorectal, endometrial and gastrointestinal cancers, but also less commonly appear in cancers arising in the breast, prostate, bladder, thyroid gland and other places. Approximately 5 percent of patients with metastatic colorectal cancer have MSI-H or dMMR tumors.

Keytruda works by targeting the cellular pathway known as PD-1/PD-L1 (proteins found on the body's immune cells and some cancer cells). By blocking this pathway, Keytruda may help the body's immune system fight the cancer cells. The FDA previously approved Keytruda for the treatment of certain patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma.

EX2004

FDA NEWS RELEASE

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

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May 23, 2017

"This is an **important first for the cancer community**," said Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now **approved a drug based on a tumor's biomarker** without regard to the tumor's original location."

POR, 71–72

JHU's Invention Changed Standard of Care for CRC



EX2163 (Neugut Dep.),
82:21–83:11

- Q. After you saw the **2015 New England Journal of Medicine article** and once **pembrolizumab was approved for MSI high colorectal cancer patients**, you **changed your practice for those MSI high cancer patients**?
- A. **That is correct.**
- Q. And why did you do that?
- A. I mean, it's clear that -- well, two reasons. One is the **obvious efficacy of the drug in that context**, and the second is it's actually a much more tolerable regime. Patients are much happier getting an immunotherapeutic agent than a conventional chemotherapy.

Oncology Community Lauded JHU's Invention

REVIEW ARTICLE

Open Access



Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease

Journal for ImmunoTherapy of Cancer (2018) 6:35

Michael M. Boyiadzis¹, John M. Kirkwood², John L. Marshall³, Colin C. Pritchard⁴, Nilofer S. Azad⁵ and James L. Gulley^{6*}

cacy. However, this marks the first tissue-agnostic approval of any drug and thus represents a **paradigm shift**, as oncologic diseases may now be classified by either tumor biomarker status or tumor histogenesis. Here we discuss the implications of this novel biomarker-based disease classification for cancer immunotherapy research and practice.

than histology-specific status. The FDA approval of pembrolizumab for advanced MSI-H/dMMR-positive solid tumors is a **tipping point** for disease reclassification based on tumor-specific factors, and propels oncology further toward the goal of precision medicine. Biomarker-based

Boyiadzis et al. *Journal for ImmunoTherapy of Cancer* (2018) 6:35
https://doi.org/10.1186/s40425-018-0342-x

Journal for ImmunoTherapy
of Cancer

REVIEW ARTICLE

Open Access

Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease

Michael M. Boyiadzis¹, John M. Kirkwood², John L. Marshall³, Colin C. Pritchard⁴, Nilofer S. Azad⁵ and James L. Gulley^{6*}

Abstract

The U.S. Food and Drug Administration (FDA) recently approved pembrolizumab, an anti-programmed cell death protein 1 cancer immunotherapeutic, for use in advanced solid tumors in patients with the microsatellite-high/DNA mismatch repair-deficient biomarker. This is the first example of a tissue-agnostic FDA approval of a treatment based on a patient's tumor biomarker status, rather than on tumor histology. Here we discuss key issues and implications arising from the biomarker-based disease classification implied by this historic approval.

Keywords: DNA mismatch repair, Microsatellite instability, Pembrolizumab, Biomarker, Immunotherapy

Background

The discovery and validation of immune checkpoints (signal-transducing pathways that modulate immune system activity) as therapeutic targets has transformed cancer immunotherapy [1]. The heavily studied immune system checkpoint, programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) regulates T-cell function through the T-cell PD-1 receptor and the PD-L1 presented by targeted cells [1, 2]. Interactions between PD-1 and PD-L1 primarily inactivate CD28 signaling to suppress T cell activation [3]. Many approved immunotherapies inhibit PD-1/PD-L1 interactions in order to stimulate an immune response against cancer cells [2].

Pembrolizumab (KEYTRUDA[®], Merck & Co, Inc., Kenilworth, NJ) is a humanized, mouse-derived anti-PD-1 antibody that promotes tumor-cell apoptosis by binding to T-cell PD-1 receptors and disrupting interaction with PD-L1 molecules on tumor cells [4, 5]. Pembrolizumab is approved for use in patients with melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, and gastric/esophagogastric junction cancer [4].

There are multiple immunological factors that potentially contribute to pembrolizumab's efficacy in subsets of patients with melanoma or NSCLC, among other cancers. Studies have noted that both melanoma and NSCLC display increased tumor immune infiltrate and PD-L1 expression [6–9]. Synergy exists between these two factors as well, as increased IFN- γ release by infiltrating immune cells can upregulate PD-L1 expression [10]. Additionally, melanoma and NSCLC are diseases that display increased tumor mutational rate and burden due to both environmental and behavioral factors. Increased tumor mutational burden can promote increased neoantigen expression, which promotes T cell expansion and recruitment [11, 12]. Thus, data supports a hypothesis that anti-PD-1 therapy may be more effective in tumors increased in mutational burden, but this has not been experimentally verified.

Cancer biomarkers are specific DNA/RNA/protein features that correlate with either risk of cancer progression (prognostic) or response to a specific therapy (predictive). Identification of cancer biomarkers has been a significant factor in recent changes in disease classification and therapy [13]. Two common predictive biomarkers, which are often found together, are tumor microsatellite instability (MSI) and DNA mismatch repair deficiency (dMMR). The dMMR biomarker indicates whether a tumor's DNA mismatch repair (MMR) system is deficient (d), based on the

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EX2089, 2, 5

Objective Indicia Show '393 Patent Non-Obvious

✓	Long-Felt Need
✓	Unexpected Results
✓	Industry Praise
✓	Commercial Success
	Skepticism

No Keytruda® MSI-H CRC Sales But For JHU's Invention

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.
U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
Issue Date: February 28, 2023
Appl. Serial No.: 17/465,101
Filing Date: September 2, 2021
Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. RICHARD GOLDBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: October 4, 2024

By: Richard Goldberg
Richard Goldberg, M.D.

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JHU 2090
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EX2090, ¶ 71

71. Prior to the May 2017 approval of the MSI-H indication, Keytruda was not approved for any indications that allowed for the treatment of colorectal cancer patients. Practically, this meant that doctors would not prescribe Keytruda to CRC patients outside of the context of a clinical trial.⁵⁸ Without an approved indication for CRC, Merck was not able to market Keytruda for use by doctors to treat CRC cancer. As a result, sales of Keytruda made to treat CRC would necessarily be sales to treat MSI-H CRC.

POR, 90; see also EX2090, ¶¶ 66–77

Merck Economic Expert's Criticisms Ring Hollow

- Dr. Sheridan provided:
 - No analysis*** of other patents purportedly covering Keytruda® or their economic impact
 - No explanation*** why third parties such as JHU would be deterred from developing the claimed method
 - No explanation*** of how his criticisms would affect Keytruda®'s commercial success in the MSI-H population
 - No quantification*** of any purported effects from “brand recognition” or “halo effect” on MSI-H CRC sales

Sur-Reply, 27–28; EX1151; EX2411, 23:4–11, 53:21–54:23, 81:1–13

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✓	Commercial success
✓	Skepticism

BMS Passed On JHU Study Due to Skepticism

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. Patent No.: 11,591,393 Attorney Docket No.: 52261-0005IP1
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Title: CHECKPOINT BLOCKADE AND
MICROSATELLITE INSTABILITY

DECLARATION OF DR. NILS LONBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/24 By: 
Nils Lonberg, Ph.D.

JHU 2072
Merck Sharp v. Johns Hopkins
IPR2024-00240

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merits of JHU's proposed study. At the time, I acknowledged that the trial would be very risky, but feeling the potential upside of a positive result could justify this risk, I reached out to several people within Bristol-Myers Squibb to advocate for our involvement in JHU's study. Nevertheless, my efforts were unsuccessful and **the skepticism among decisionmakers within Bristol-Myers Squibb prevailed**. In other words, **Bristol-Myers Squibb passed up on the opportunity to be involved in JHU's MSI-H trial not once, but *multiple times* after careful consideration**. This skepticism is directly related to the claims of the '393 Patent since it related to the very MSI-H

EX2027, ¶ 186

POR, 74-75

Merck Executive Admitted Skepticism



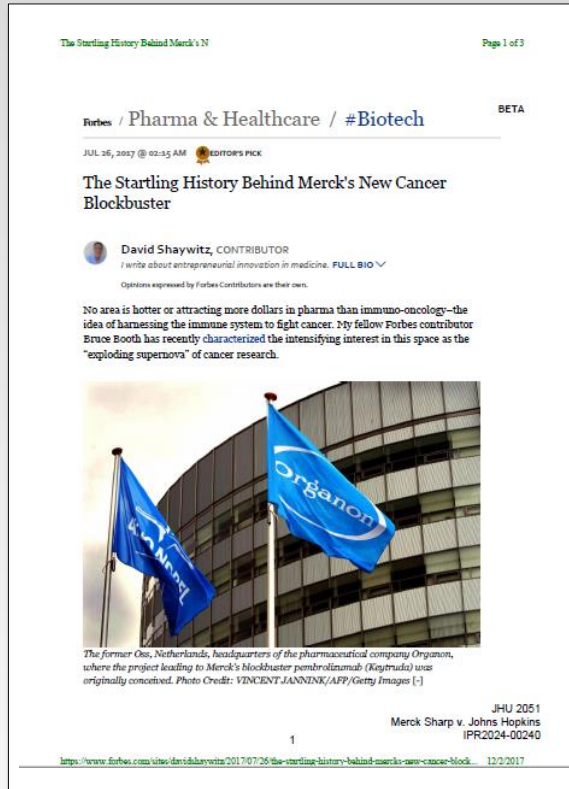
EX2121,17

But I think one of the things I'll comment on that I think is very interesting about it, is there have been prior small numbers of colon cancer patients who'd been treated with anti-PD-1 agents, and the responses were pretty much zero, and so the idea was, early on, that it really wasn't going to work in colon cancer, as a monotherapy.

- Eric Rubin, VP Global Clinical Oncology,
Merck Research Laboratories

POR, 74-75

For Tissue-Specific Cancers, Merck Effectively Gave Its Scientists a Blank Check: “There Is No Line”



EX2051, 15–16

“There Is No Line”

While the pembro clinical development program began under Kim, and was even placed on accelerated or “gold track” status internally, the key impact Perlmutter had on the program was recognizing it as an exceptional asset and redirecting virtually all work at Merck towards this program. According to Perlmutter, “I told everyone in research: stop what you’re doing now. We’ve got to do this.”

The organization got the message, and stories of Perlmutter’s emphasis on Keytruda abound. According to one scientist, Perlmutter reportedly said, “I don’t want to wake up in five years and wish I blew another \$1 billion on this drug.” Former Merck executive Reicin recalls presenting Perlmutter with a prioritized list of potential Keytruda clinical studies and asking him, based on resources, where to draw the line. “There is no line,” Perlmutter reportedly responded. “Do them all.”

POR, 74

Yet Merck Initially Declined to Fund JHU's Clinical Trial

Case 1:22-cv-03059-BPG Document 1-3 Filed 11/29/22 Page 2 of 16

INVESTIGATOR INITIATED CLINICAL TRIAL RESEARCH AGREEMENT (US Single Site - Study Drug)

This Agreement is entered into as of the last date on the signature page hereof, by and between THE JOHNS HOPKINS UNIVERSITY having a School of Medicine with an Office of Research Administration located at 733 North Broadway, Suite 117, Baltimore, MD 21205, hereinafter called "Institution," and MERCK SHARP & DOHME CORP. with its address at One Merck Drive, Whitehouse Station, New Jersey 08889 USA, hereinafter called "Merck."

Principal Investigator (named in Article 2 below) and Institution desire to sponsor and conduct a study of the safety and/or efficacy of MK-3475 which may be or include a pharmaceutical product, biological product, device or diagnostic agent provided to Institution hereunder (the "Study Drug") through certain clinical research in accordance with the Protocol identified below (the "Study"). Merck, consistent with its commitment to clinical research, wishes to provide certain support to Institution on the terms and conditions described in this Agreement. The parties hereto agree as follows:

1. Scope of Work

The Institution and Principal Investigator (named in Article 2 below) shall perform the Study in accordance with the terms of this Agreement and the final protocol including as it may be amended in accordance with the terms of this Agreement, for the Study entitled "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors" Protocol Number MK-3475-016 (the "Protocol") MSP Database number 50642, which has been accepted by Merck in writing and incorporated into this Agreement by reference. Institution represents and warrants that, to its best knowledge, its facilities and patient population are adequate to perform the Study contemplated by this Agreement and the Protocol. Institution and Principal Investigator agree that all aspects of the Study will be conducted in conformity with all applicable federal, state, local laws and regulations. Institution and Principal Investigator further agree not to conduct any research activities with the Study Drug which are contrary to the provisions of the Protocol or outside the scope of the Protocol. Principal Investigator (or Institution) will undertake the Study as the legal sponsor of the Protocol and will fulfill the requisite sponsor duties and obligations in conducting the Study.

2. Principal Investigator

Institution's principal investigator is Dung Thi Le, MD ("Principal Investigator"). Principal Investigator will be responsible for the direction and supervision of all Study efforts, in accordance with the Protocol and this Agreement. Principal Investigator and Institution shall provide all of the services contemplated herein through fully trained and competent Study Staff (as defined below) having a skill level appropriate for the tasks assigned to them and shall ensure that all Study Staff (as defined below) comply with the terms of this Agreement and the Protocol. "Study Staff" means any persons providing services on behalf of Institution in connection with the Study, and may include: (i) employees, agents, officers, and directors of Institution, including without limitation the Principal Investigator, and (ii) any contractors or other third parties approved by Merck in writing in

7. Funding

No Funding shall be provided by Merck under this Agreement. Merck acknowledges that the Study is being funded by Swim Across America, who may have access to the results of the Study.

EX2131, 8

POR, 74; Sur-Reply, 22-23

Objective Indicia Show '393 Patent Non-Obvious

✓	Long-Felt Need
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