Petitioner Demonstratives

Merck Sharp & Dohme LLC v. The Johns Hopkins University

Inter Partes Review of U.S. Patent No. 11,591,393
Case No. IPR2024-00240

Oral Hearing: March 31, 2025

[DEMONSTRATIVE EXHIBIT – NOT EVIDENCE]

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MERCK EX1239

Instituted Grounds

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Instituted Grounds

		Claims
Ground 1	**Anticipation** MSI-H Study Record (MSR)	1-2, 4-7, 11-12, 14-15, 17-20, 24-25, 27-42
Ground 2	**Obviousness** MSR in view of Pernot	1-2, 4-7, 11-12, 14-15, 17-20, 24-25, 27-42
Ground 3	**Obviousness** MSR, or MSR in view of Pernot, in view of Chapelle	2, 8, 15, 21
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Ground 8	**Obviousness** MSR, or MSR in view of Pernot, in view of Steinert and Hamid	13 and 26

MERCK EX1239

The Challenged Claims

All Challenged Claims Are Directed to a Two-Step Method for Treating a MSI-H Cancer Patient with Pembrolizumab

'393 Patent at Claim 1

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.

EX1001 Claim 1.

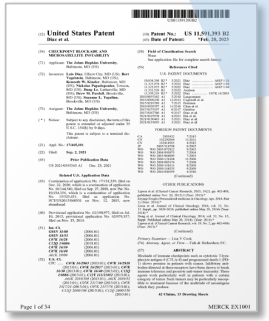
'393 Patent at Claim 14

14. A method of reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer, 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.

EX1001 Claim 14.


United States Patent

Pet. at 5, 20-23, 29.

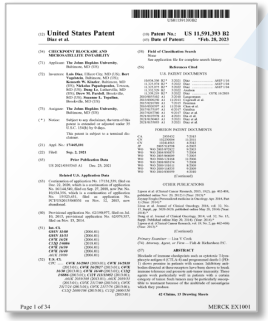
Dependent Claims Directed to Natural Results That Flow from Carrying Out the Claimed Two-Step Method

'393 Patent at Claims 31, 33, 35

31. The method of claim **1**, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.

33. The method of claim **1**, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.

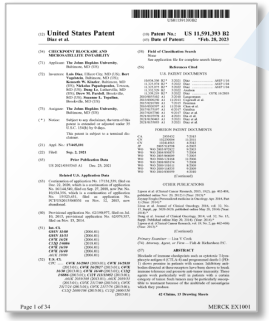
35. The method of claim **1**, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.


United States Patent

EX1001 Claims 31, 33, 35, *see also* Claims 37, 39, 41.

Pet. at 15-18, 33-36.

Certain Dependent Claims Specify Method Details Indisputably Well Understood and Known by a POSA


United States Patent

Mao et al.

Patent No.: US 11,591,393 B2

Date of Patent: *Feb. 28, 2023

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'393 Patent at Claims 2, 3, 8, 9 10

2. The method of claim **1**, wherein the biological sample is a tumor tissue from the patient.

EX1001 Claim 2, *see also* Claim 15.

3. The method of claim **1**, wherein the biological sample is a body fluid from the patient.

EX1001 Claim 3, *see also* Claim 16.

8. The method of claim **1**, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample.

EX1001 Claim 8, *see also* Claim 21.

9. The method of claim **1**, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample.

EX1001 Claim 9, *see also* Claim 22.

10. The method of claim **1**, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample.

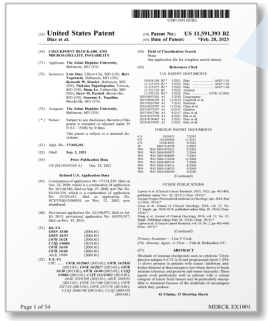
EX1001 Claim 10, *see also* Claim 23.

Pet. at 46-50, 58-60.

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Certain Dependent Claims Specify Generally Understood Standards of Care

'393 Patent at Claims 7, 29, 30, 32


United States Patent
Mace et al.
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Feb. 28, 2023
MERCK EX1001

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.

EX1001 Claim 7, *see also* Claim 20.

29. The method of claim **1**, wherein the colorectal cancer is metastatic colorectal cancer.

EX1001 Claim 29.

30. The method of claim **14**, wherein the colorectal cancer is metastatic colorectal cancer.

EX1001 Claim 30.

32. The method of claim **31**, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.

EX1001 Claim 32, *see also* Claims 34, 36, 38, 40, 42.

Pet. at 25-27, 31-33, 50-56.

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Anticipation

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Disputed Issues

- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

  (only Claims 31, 33, 35, 37, 39, 41)
- disclosure of prior cancer therapy

  (only Claims 7, 20, 32, 34, 36, 38, 42)
- disclosure of treating a metastatic colorectal cancer patient

  (**only Claims 29, 30**)

Disputed Issues

- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

  (**only Claims 31, 33, 35, 37, 39, 41**)
- disclosure of prior cancer therapy

  (**only Claims 7, 20, 32, 34, 36, 38, 42**)
- disclosure of treating a metastatic colorectal cancer patient

  (**only Claims 29, 30**)

Experimental Use Exception Is Not Applicable for Printed Publication

- Study records on ClinicalTrials.gov can be relied on for anticipation and obviousness

  Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, IPR2022-00578, Paper 78 at 24-28 (P.T.A.B. Aug. 29, 2023)

  Salix Pharms., Ltd. v. Norwich Pharms. Inc., 98 F.4th 1056, 1061 (Fed. Cir. 2024)

- JHU's cited cases **do not** support its proposed experimental use exception

  City of Elizabeth v. Am. Nicholson Pavement Co., 97 U.S. 126, 133-36 (1877)

  Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1352-55 (Fed. Cir. 2002)

  Paeco, Inc. v. Applied Moldings, Inc., 562 F.2d 870, 872 (3d Cir. 1977)

  Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1380-81 (Fed. Cir. 2006)

Reply at 17-20.

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If JHU Believed It Had a Patentable Invention Requiring Results, It Could Have Filed Within the Allotted One-Year Period

JHU Declarant Dr. Le at 291:7-19

Q So in your Declaration you testified, quote, the data we obtained from our initial small study were, end quote. So I'm trying to find out what data was that.

A The responses, or the -- that here we say anecdotally our patients felt better. So there was different kinds of data.

Q And what was the time frame of this data that you're referencing in your Declaration?

A The time frame of the data. The data we obtained from our initial -- again, it's the early patients, what happened to the patients who were early in the study.

EX1139 (Dr. Le Dep. Tr.) at 291:7-19.

Reply at 17-20.

MERCK EX1239

Disputed Issues

- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

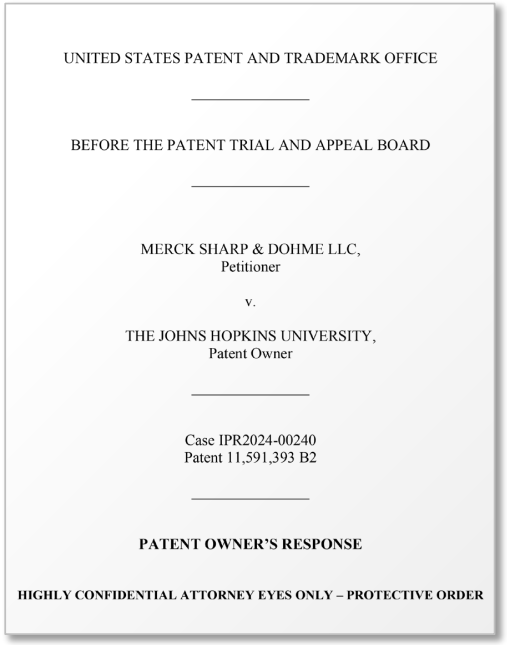
  (**only Claims 31, 33, 35, 37, 39, 41**)
- disclosure of prior cancer therapy

  (**only Claims 7, 20, 32, 34, 36, 38, 42**)
- disclosure of treating a metastatic colorectal cancer patient

  (**only Claims 29, 30**)

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JHU's Unsupported Arguments Regarding "In Response To"



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Patent 11,591,393 B2

PATENT OWNER'S RESPONSE

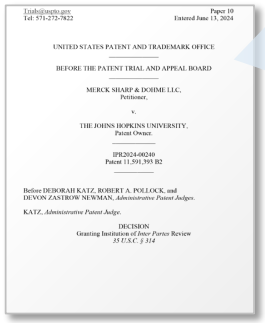
HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

- The Board's claim construction at Institution was erroneous
- The MSR does not disclose a causal relationship between testing and treating a patient
- The MSR describes an "all-comers" study that allows determining MSI-H status after a patient is treated with pembrolizumab

POR at 1-3, 14-16.

Reply at 11-13; POR at 1-3, 14-16; *see also* EX2072 ¶¶94-99.

The Institution Decision Applied a Causal Relationship


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,
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v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

IPR2024-00240
Patent 11,591,395 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

Institution Decision at 15, 16

Patent Owner argues that there is no causal relationship described in the MSI-H Study Record between treating of colorectal cancer patients and determining their MSI status because all patients were treated with pembrolizumab and MSI status was only described after enrollment in order to assign a patient to a cohort. (*See* Prelim. Resp. 42–43.) Again, Patent Owner focuses on the design of the study, not what the study describes as the actual treatment of microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient.

(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.

Paper 10 at 15, 16.

Reply at 8-10; Paper 10 at 15, 16.

MERCK EX1239

The Institution Decision Recognized the Temporal Limitation of the Claims

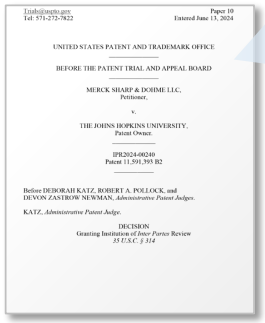
Institution Decision at 16, 17

patient was treated with pembrolizumab. (Ex. 2001 ¶ 106.) Thus, because treatment of the patient was performed only after MSI-H status was determined, the evidence of record favors Petitioner.

***

pembrolizumab." At this point in the proceeding, though, we do not interpret the claim step as meaning anything other than the treatment of colorectal cancer patients after they have been determined to be microsatellite instability high or DNA mismatch repair deficient. Although the term "in response to" in claim 1

Paper 10 at 16, 17.



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Reply at 8-10; Paper 10 at 16, 17.

JHU's Declarant Agrees That the Board Did Not Ignore the Causal Relationship in the Claims

JHU Declarant Dr. Lonberg at 125:5-14

You understand that the board did not ignore that the claim language in response to found in the claims of the '393 Patent involved a causal relationship between treatment of colorectal cancer patients and determination of their MSI-High status, right?

A That seems to be the implication because they do bring up causal relationship.

EX1138 (Dr. Lonberg Dep. Tr.) at 125:5-14.

Reply at 8-9.

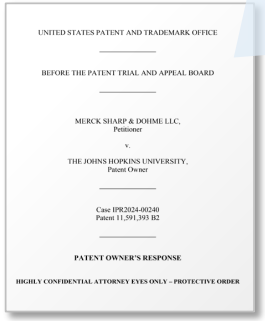
MERCK EX1239

JHU's Flawed Interpretation of the Institution Decision as to Claim Construction

Patent Owner Response at 6

> the claims. The express causal relationship between these steps establishes that ***only*** CRC patients determined to be MSI-H are treated. This critical aspect of the claimed invention is omitted by the Board's construction.

POR at 6.



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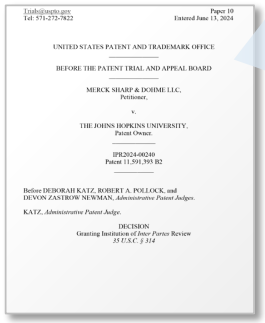
Case IPR2024-00240
Patent 11,591,393 B2

PATENT OWNER'S RESPONSE

HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER

Reply at 9; Paper 10 at 15-16.

The Institution Decision Correctly Rejected JHU's Attempt to Insert a Negative Limitation into the Claims


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Institution Decision at 17, 18

DNA mismatch repair deficient. Although the term "in response to" in claim 1 requires that treatment of the patient occur after the determination that the colorectal cancer is MSI-H, we do not interpret the term to mean that other patients are not treated or that the recruitment and enrollment of patients for a clinical trial has any bearing on the steps recited in claim 1.

claim 1. At this point in the proceeding, we construe the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients.

Paper 10 at 17, 18.

Reply at 8-10; Paper 10 at 17, 18.

The MSR Published by June 12, 2013 and Includes the Claimed Two-Step Treatment Method

MSR at 1, 3

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

Submitted Date	Changes
June 10, 2013	None (earliest Version on record)

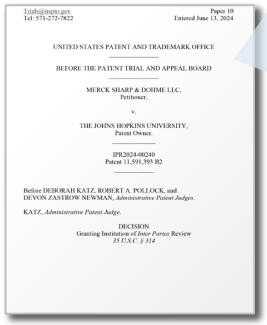
Sponsor/Collaborators

Sponsor: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Responsible Party: Sponsor

Collaborators: Merck Sharp & Dohme LLC

EX1005 at 1, 3.



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KATZ, *Administrative Patent Judge*.

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Pet. at 7-10.

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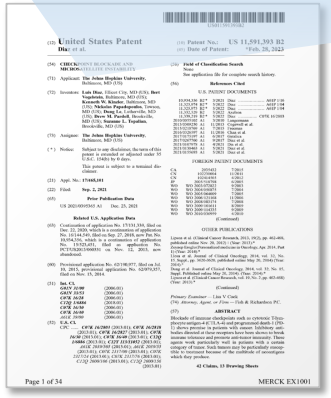
First Claim Step: Test a Patient to Determine Their MSI-H Status

'393 Patent at Claim 1

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

EX1001 Claim 1.

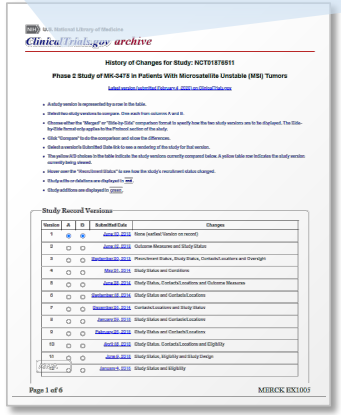


MSR at 5

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer

EX1005 at 5.



Pet. at 20-21; Reply at 10-14.

MERCK EX1239

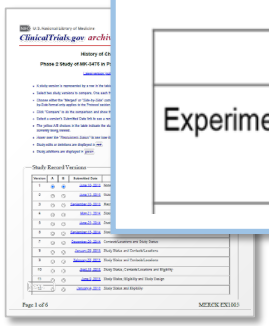
The MSR Teaches Testing a Patient to Determine Their MSI-H Status Prior to Treatment

MSR at 1, 4, 5

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

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer



▼ Arms and Interventions

Arms
Experimental: MSI Positive Colorectal Cancer

▼ Conditions

Conditions: MSI Positive Colorectal Cancer
MSI Negative Colorectal Cancer
MSI Positive Non-Colorectal Cancers

EX1005 at 1, 4, 5.

Pet. at 20-21; Reply at 10-14.

MERCK EX1239

MSI-H Status Must First Be Determined for Placement of MSI-H CRC Patient in the Proper Arm for Treatment

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶¶62, 63

62. The Inclusion Criteria, however, that Dr. Neugut points to in this section of his declaration discusses that MSI-H colorectal cancer patients can be placed ***only*** in the arm of the study that is composed of patients having MSI-H colorectal cancer. (*See* EX1005 at 5 (Inclusion Criteria) ("1. Arm 1 only: Patients

63. Contrary to Dr. Lonberg's assertion, the MSI-H Study Record also discussing one arm of the study being entirely composed of patients with colorectal cancer that is not MSI-H actually further supports the need to first determine the colorectal cancer patient's MSI status to place the patient into the proper arm of the study. (*See* EX1003, ¶¶58-63; EX2072, ¶¶92-93; *see also* EX1005, 4 (Arms and

EX1150 ¶¶62, 63.

Reply at 10, 12.

MERCK EX1239

Second Claim Step: In Response to Determining the Patient Is MSI-H, Give the Patient an Effective Amount of Pembrolizumab

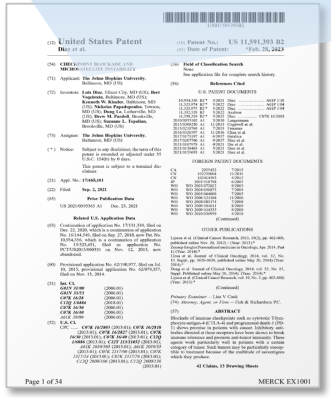
'393 Patent at Claim 1

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

* * *

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.

EX1001 Claim 1.

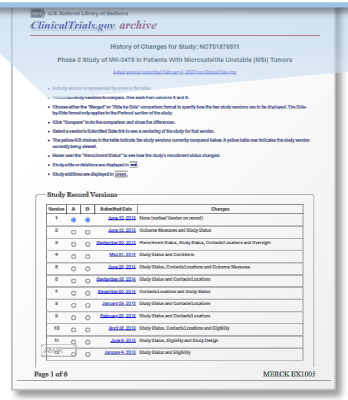


MSR at 4

▼ 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

EX1005 at 4.



Pet. at 21-23.

MERCK EX1239

The MSR Teaches Treating a Patient in Response to Determining the Patient is MSI-H

MSR at 4, 5

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer


ClinicalTrials.gov archive

History of Changes for Study: NCT01876011

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

Study Record Versions

Page 1 of 6

MERCK EX1002

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

EX1005 at 4, 5.

Pet. at 21-23.

MERCK EX1239

Dr. Lonberg's "All-Comers" Argument Illogically Ignores the MSR Study Design and Low Incidence of MSI-H CRC

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶¶67, 68

67. Further, the MSI-H Study Record describes in the Study Design section that the allocation of patients in the arms of the study is non-randomized. (EX1005, 4 (Study Design).) Therefore, the POSA would understand that patients could not be "randomly assigned [to receive treatment] regardless of biomarker status" as Dr. Lonberg asserts. (EX2072, ¶97.)

68. Additionally, the MSI-H Study Record describes in the Study Design section that the anticipated enrollment of the study is 71 patients. (EX1005, 4 (Study Design).) Given the low incidence of MSI-H in the colorectal cancer population (about 15%), and even lower in the metastatic colorectal cancer population that would be treated in the MSI-H Study, the POSA would understand that the MSI-H Study Record requires that a patient is tested to determine whether the patient is MSI-H before being enrolled and treated in the study. (*See* EX2072,

EX1150 ¶¶67, 68.

Reply at 13.

MERCK EX1239

MSR Study Design Allocation
Non-Randomized and Only Enrolled 71 Patients

MSR at 4


U.S. National Library of Medicine
ClinicalTrials.gov archive
History of Changes for Study: NCT01876011
Phase 2 Study of MK-0475 in Patients With Microsatellite Unstable (MS) Tumors
Study Record Versions:
Page 1 of 6
MERCK EX1002

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Non-Randomized
Enrollment:	71 [Anticipated]

EX1005 at 4.

Reply at 13; EX1150 ¶68.

Dr. Goldberg Admitted That at Least a Patient's MSI-H Status Had to Be Known to Be MSI-H Before Treatment

JHU Declarant Dr. Goldberg at 67:4-68:3

Q How would a patient with MSI-high cancer have been placed into the MSI cohorts of the 2013 MSI-high study without being tested for MSI-high?

A So in all three arms, arms A, B and C were open, patients were allowed to enroll in the study whether they were MSI-high or MSS. And because the treatment was the same regardless of whether they were MSI-high or MSS, patients could be enrolled in the study without knowledge of their microsatellite instability status and would be assigned to the correct arm of the study only after their tumors have been tested for microsatellite instability until such time as the MSS cohort in the basket study had met its full accrual goals.

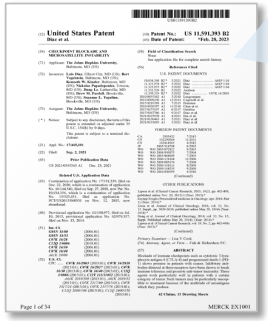
After that, in order to be eligible for the study, a colorectal cancer patient had to be known to be MSI-high and a non-colorectal cancer patient had to be known to be MSI-high. But at the time that the study initially opened, accrual could proceed before MSI status was known.

EX1136 (Dr. Goldberg Dep. Tr.) at 67:4-68:3.

Reply at 13-14.

MERCK EX1239

The Only Description of Cancer Patients' Treatments in the Patent Specification Is the Cancer Patients' Treatments in the MSR



'393 Patent Specification at 6:52-56, 8:50-53

The data from the small phase 2 trial of pembrolizumab to treat tumors with and without deficiency of MMR supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors. MMR-deficiency occurs in many cancers, including

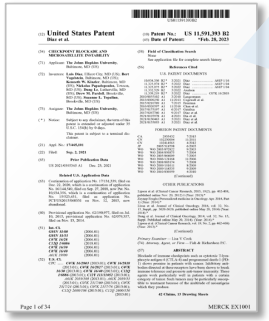
EX1001 at 6:52-56.

This phase 2 trial was conducted using a Green-Dahlberg two-stage design and consisted of the three parallel cohorts described above. The study agent, pembrolizumab (Merck), was administered at 10 mg/kg intravenously every 14 days.

EX1001 at 8:50-53.

Pet. at 9, 22; Reply at 9.

The Only Description of Cancer Patients' Treatments in the Patent Specification Is the Cancer Patients' Treatments in the MSR



'393 Patent Specification at 8:29-36, 13:27-30

It consisted of two-stage phase 2 studies in parallel in the three cohorts of patients described in the text. The study agent, MK-3475, was administered at 10 mg/kg intravenously every 14 days.

EX1001 at 13:27-30.

Treatment-refractory progressive metastatic cancer patients for this phase 2 study were recruited from three participating centers (Table 1). Three cohorts were evaluated: Cohort A was composed of patients with MMR-deficient colorectal adenocarcinomas; Cohort B was composed of patients with MMR-proficient colorectal adenocarcinomas; and Cohort C was composed of patients with MMR-deficient cancers of types other than colorectal.

EX1001 at 8:29-36.

Pet. at 9, 22; Reply at 9.

MERCK EX1239

JHU's Declarant Acknowledges the Relationship Between the MSR and the '393 Patent

JHU Declarant Dr. Lonberg at ¶110

> 110. With respect to claims 4 and 17, the amount of pembrolizumab used for the claimed treatment method specifically requires being "shown in a clinical trial" to achieve particular results. And with respect to claims 31, 33, 35, 37, 39, and 41, the results recited in the claims correspond directly with the outcome measures obtained by the trial described in the MSI-H Study Record.

EX2072 ¶110.

Reply at 16.

MERCK EX1239

Disputed Issues

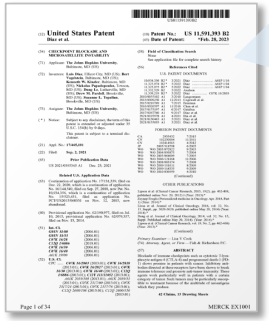
- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

  (only Claims 31, 33, 35, 37, 39, 41)
- disclosure of prior cancer therapy

  (only Claims 7, 20, 32, 34, 36, 38, 42)
- disclosure of treating a metastatic colorectal cancer patient

  (only Claims 29, 30)

Dependent Claims 31, 33, and 35 Are Directed to the Natural Results That Flow from Carrying Out the Claimed Two-Step Method


United States Patent

Mier et al.

Patent No.: US 11,591,393 B2

Date of Patent: *Feb. 28, 2023

MERCK EX1001

'393 Patent at Claims 31, 33, 35

31. The method of claim **1**, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.

33. The method of claim **1**, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.

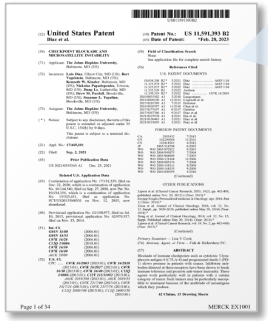
35. The method of claim **1**, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.

EX1001 Claims 31, 33, 35.

Pet. at 33-36; EX1003 ¶¶92, 95, 97.

MERCK EX1239

Dependent Claims 37, 39, and 41 Are Directed to the Natural Results That Flow from Carrying Out the Claimed Two-Step Method


United States Patent

Page 1 of 34

MERCK EX1001

'393 Patent at Claims 37, 39, 41

37. The method of claim **29**, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.

39. The method of claim **29**, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.

41. The method of claim **29**, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.

EX1001 Claims 37, 39, 41.

Pet. at 36-37; EX1003 ¶¶99, 101, 103.

MERCK EX1239

The MSR's Disclosure of the Claimed Two-Step Treatment Method Inherently Discloses the Results of That Method

Schering at 1379

- Prior art disclosed a method of treatment of administering loratadine, an antihistamine
- The disclosure inherently anticipated patent claims directed to loratadine's metabolite naturally produced *in vivo*
- At the time of the filing of the metabolite patent:
  - the loratadine method had not been practiced
  - the metabolite was neither disclosed in the prior art or even in actual existence

Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1374, 1378-79 (Fed. Cir. 2003).

Pet. at 17; Reply at 15.

MERCK EX1239

Application of Inherent Anticipation: Clinical Trials

Montgomery at 1381

- The prior art disclosed a planned clinical study
- The court found the disclosure anticipated method of treatment claims

> "[E]ven if [the documents disclosing the planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate."

> "[E]ven if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps."

In re Montgomery, 677 F.3d 1375, 1381 (Fed. Cir. 2012).

Pet. at 17; Reply at 15.

MERCK EX1239

JHU Continues to Erroneously Focus on the Results of the MSR Treatment Method in Arguing for Patentability

JHU Sur-Reply at 5

> claims." Reply, 4, 9, 16. The written description support for the claimed method of treatment is not the MSR, but the ***results*** of the clinical study conducted pursuant to the MSR and its many subsequent amendments. *See* EX1001, Figs. 1-

Sur-Reply at 5.

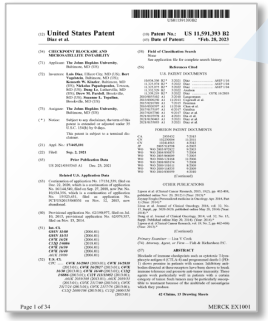


"Because ***inherency places subject matter in the public domain*** as well as an express disclosure, the inherent disclosure of the entire claimed subject matter anticipates as well as inherent disclosure of a single feature of the claimed subject matter . . . . a ***limitation or the entire invention is inherent*** and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art."

Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

Pet. at 9, 15-17; Reply at 15-16.

JHU Erroneously Focused on the Results of the MSR Treatment Method in Arguing for Patentability


United States Patent

Page 1 of 34

MERCK EX1001

'393 Patent at 3:19-21, 6:52-56

To test this hypothesis, we initiated a phase 2 clinical trial to evaluate immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency. Since MMR

EX1001 at 3:19-21.

The data from the small phase 2 trial of pembrolizumab to treat tumors with and without deficiency of MMR supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors. MMR-deficiency occurs in many cancers, including

EX1001 at 6:52-56.

Pet. at 9.

MERCK EX1239

Disputed Issues

- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

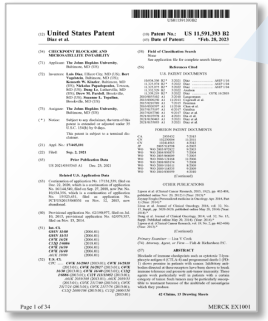
  (only Claims 31, 33, 35, 37, 39, 41)
- disclosure of prior cancer therapy

  (only Claims 7, 20, 32, 34, 36, 38, 42)
- disclosure of treating a metastatic colorectal cancer patient

  (only Claims 29, 30)

MERCK EX1239

Dependent Claims 7, 20, 32, 34, 36, 38, 40, 42 Specify Generally Understood Standards for Cancer Patients to Be Treated


United States Patent

Pet. at 25-27, 30, 34-37, 50-57.

'393 Patent at Claims 7, 32

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.

EX1001 Claim 7, *see also* Claim 20.

32. The method of claim **31**, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.

EX1001 Claim 32, *see also* Claims 34, 36, 38, 40, 42.

MERCK EX1239

The MSR Reflects That It Is a Clinical Study Appropriate for a Patient That Would Have Had Prior Cancer Treatments

MSR at 5-6

Exclusion Criteria:

1. Currently have or have history of certain study-specified heart, liver, kidney, lung, neurological, immune or other medical conditions
2. Systemically active steroid use
3. Patients on home oxygen
4. Patients who have had prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies
5. Another investigational product within 28 days prior to receiving study drug
6. Pregnant or lactating
7. Conditions, including alcohol or drug dependence, or intercurrent illness that would affect the patient's ability to comply with study visits and procedures

EX1005 at 5-6.


ClinicalTrials.gov archive

History of Changes for Study: NCT01876011

Phase 2 Study of MK-0475 in Patients With Microsatellite Unstable (MS) Tumors

Study Record Versions:

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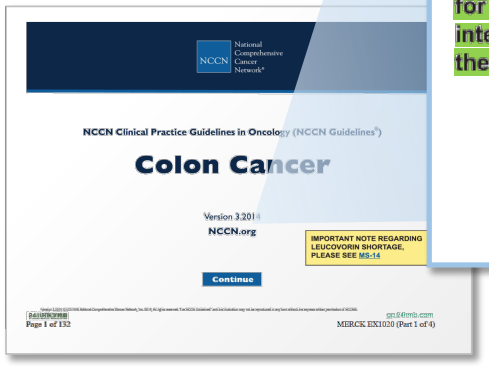
MERCK EX1002

Pet. at 25-27; EX1003 ¶¶68-72; EX1150 ¶¶76-77.

MERCK EX1239

Clinical Trials Recommended Only After Second and Third Progression of Advanced or Metastatic Colon Cancer

NCCN Guidelines at 25



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014 Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 9)

Initial Therapy	Therapy After First Progression	Therapy After Second Progression	Therapy After Third Progression
Patient appropriate for intensive therapy[2]	FOLFOX[3] ± bevacizumab or CapeOX[4] ± bevacizumab[5,6] or FOLFOX[3] ± panitumumab[6,7] (KRAS/NRAS WT gene only)[8,9]	FOLFIRI[5,10] ± bevacizumab or FOLFIRI ± ziv-aflibercept[11] or Irinotecan[10] ± bevacizumab or Irinotecan[10] ± ziv-aflibercept[11] or FOLFIRI + (cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] or (Cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] + irinotecan[10]	(Cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] + irinotecan;[10] for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] or Regorafenib[16] Regorafenib or Clinical trial or Best supportive care[17]	Regorafenib (if not given previously) or Clinical trial or Best supportive care[17]

EX1020 at 25.

Pet. at 25-26, 32; EX1003 ¶¶51, 69-70, 88.

The MSR Requires Treating Patients Who Failed Prior Therapies

Alfred I. Neugut, M.D.



Medical Oncologist
Herbert Irving Comprehensive Cancer Center,
Columbia University

Merck Declarant Dr. Neugut ¶70

70. Patients with metastatic and advanced cancer that would participate in a clinical study, like the MSI-H study (EX1005 at 2 (Study Identification), 4 (Study Design)), would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after both drug therapies. (EX1020 at PDF p. 25; *see also* EX1009 at 1034; EX1047 at 4-7.) Additionally, because such patients were specified to still have a "tumor" and "measurable disease," it would mean that the cancer had progressed following that prior treatment. Indeed, the person of ordinary skill would have found it highly unusual for that patient population, patients who had received two prior drug treatments and had their cancer progress after those treatments, to not be included in the MSI-H Study Record, particularly without any explicit carve-out.

EX1003 ¶70.

Pet. at 26; Reply at 14-15.

MERCK EX1239

Dr. Lonberg Disregards the Context of the MSR

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶76

76. Dr. Lonberg alleges that the MSI-H Study Record does not disclose that patients would have received prior drug therapies and had their cancers progress after those therapies based solely on his mischaracterization of Dr. Neugut's opinions regarding "measurable" disease. (EX2072, ¶102.) In that section of Dr. Neugut's declaration, however, he explains that the MSI-H Study Record's Eligibility Criteria requires that patients have "measurable disease," and Study Identification section mentions "tumors," and these disclosures in the *context of the MSI-H Study Record* tell the POSA that the cancer patients being treated would have received prior drug therapies and had their cancers progress after those therapies. (*See* EX1003, ¶¶68-72; *see also* EX1005, 2 (Study Identification), 5-6 (Eligibility Criteria).) Further, Dr. Neugut explains that the

EX1150 ¶76.

Reply at 14-15.

MERCK EX1239

Disputed Issues

- The MSR's status as 102(a) prior art
- "in response to" claim limitation
- inherent disclosure of treatment results

  (only Claims 31, 33, 35, 37, 39, 41)
- disclosure of prior cancer therapy

  (only Claims 7, 20, 32, 34, 36, 38, 42)
- disclosure of treating a metastatic colorectal cancer patient

  (only Claims 29, 30)

MERCK EX1239

Dependent Claims 29-30 Specify Generally Understood Standards of Care Reflected in MSR

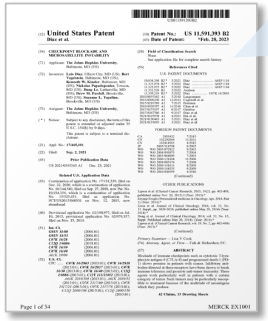
'393 Patent at Claims 29, 30

29. The method of claim **1**, wherein the colorectal cancer is metastatic colorectal cancer.

EX1001 Claim 29.

30. The method of claim **14**, wherein the colorectal cancer is metastatic colorectal cancer.

EX1001 Claim 30.


United States Patent

Pet. at 31-33, 53-55; EX1003 ¶¶87-91.

MERCK EX1239

The MSR Requires That the Patient Have Measurable Disease

MSR at 5

Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer
4. Have measurable disease

EX1005 at 5.

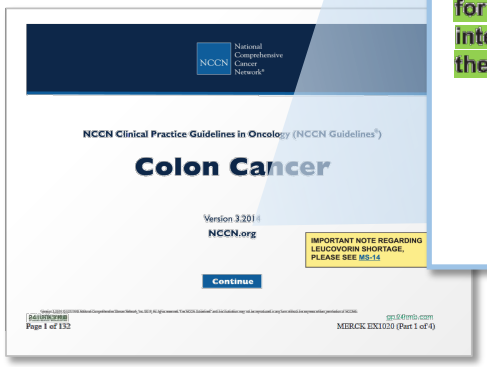

U.S. National Library of Medicine
ClinicalTrials.gov archive
History of Changes for Study: NCT01876011
Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors
Study Record Versions:
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MERCK EX1002

Pet. at 31-33; *see also id.* at 25-26; EX1003 ¶¶87-91; EX1150 ¶¶85-86.

MERCK EX1239

Clinical Trials Recommended for Advanced or Metastatic Colon Cancer Patients

NCCN Guidelines at 25



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014 Colon Cancer

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EX1020 at 25.

Pet. at 31-33; EX1003 ¶¶88-89; EX1150 at ¶¶85-86.

The MSR Requires Treating Metastatic or Advanced Stage Colorectal Cancer Patients

Alfred I. Neugut, M.D.



Medical Oncologist
Herbert Irving Comprehensive Cancer Center,
Columbia University

Merck Declarant Dr. Neugut ¶70

70. Patients with metastatic and advanced cancer that would participate in a clinical study, like the MSI-H study (EX1005 at 2 (Study Identification), 4 (Study Design)), would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after both drug therapies. (EX1020 at PDF p. 25; *see also* EX1009 at 1034; EX1047 at 4-7.) Additionally, because such patients were specified to still have a "tumor" and "measurable disease," it would mean that the cancer had progressed following that prior treatment. Indeed, the person of ordinary skill would have

EX1003 ¶70.

Pet. at 25-26.

MERCK EX1239

The MSR Requires Treating Metastatic or Advanced Stage Colorectal Cancer Patients

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶85

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 ¶85.

So again, because this wouldn't be appropriate for a newly diagnosed patient who had not had chemotherapy, essentially everyone who fit that criteria would be under the category of metastatic.

EX2404 (Dr. Oberstein Dep. Tr.) at 276:2-6.

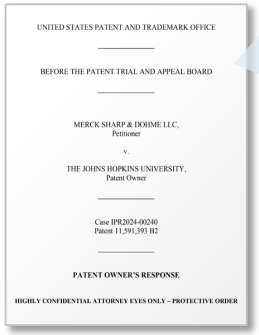
Reply at 14.

Obviousness

MERCK EX1239

Uncontested Issues

- Obviousness of all Dependent Claims if Independent Claims 1 and 14 are anticipated


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 at 57

D. Merck Has Not Shown the Dependent Claims Would Have Been Obvious Over the Prior Art in Grounds 3-8

The prior art in Grounds 3-8 does nothing to fill the Petition's deficiencies regarding either the "in response to" claim limitation or the requirement that a POSA "would have reasonably expected to achieve success in the treatment" claimed in the '393 Patent. *Eli Lilly*, 8 F.4th at 1344. Merck does not allege it does. Instead, as the DI acknowledges, Merck relies on Chapelle, Steinert, Benson, Salipante, and Hamid for discrete limitations unrelated to either issue. DI, 24-25. None renders the dependent claims unpatentable. EX2072, ¶¶74-82, 173-180.

POR at 57.

Reply at 21.

Disputed Issues

- "in response to" claim limitation and reasonable expectation of success to achieve the claimed two-step treatment method
- secondary considerations

Disputed Issues

- "in response to" claim limitation and reasonable expectation of success to achieve the claimed two-step treatment method
- secondary considerations

Grounds 2-8: All Challenged Claims Obvious Over the MSR in View of Various Prior Art

The "In Response to" Claim Limitation and Reasonable Expectation of Success to Achieve The Claimed Two-Step Treatment Method

- ✓ The MSR teaches giving an effective amount of pembrolizumab to a colorectal cancer patient in response to determining the patient is MSI-H

EX1005.

- ✓ The prior art provided additional motivation to carry out the claimed two-step treatment method

EX1006 (Pernot (April 2014)); EX1032 (Champiat (Jan. 2014)); EX1033 (Gatalica (Nov. 2014)); EX1034 (Brown (May 2014)); EX1039 (Llosa (May 2014)).

Pet. at 38-63.

MERCK EX1239

The MSR Teaches Treating a Patient with Pembrolizumab in Response to Determining the Patient Is MSI-H

MSR at 1, 5

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

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer

EX1005 at 1, 5.


U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT01876011

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

Study Record Versions:

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MERCK EX1002

Pet. at 18-23; EX1003 ¶¶37, 50, 53-63; *see also* EX1151 ¶¶61-70.

The MSR Teaches Treating a Patient with Pembrolizumab in Response to Determining the Patient Is MSI-H

MSR at 4

▼ **Arms and Interventions**

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

▼ **Outcome Measures**

Primary Outcome Measures:

1. Immune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)
   [Time Frame: 4 years]

2. Objective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)
   [Time Frame: 4 years]


ClinicalTrials.gov archive

History of Changes for Study: NCT01876011

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

MERCK EX1002

EX1005 at 4.

Pet. at 18-23; EX1003 ¶¶37, 50, 53-63; *see also* EX1151 ¶¶61-70 .

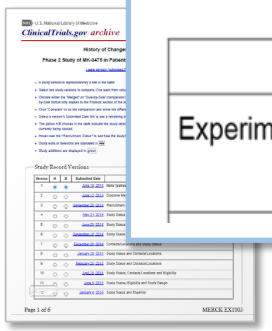
The MSR Provides a Reasonable Expectation of Success for the First Step of the Claimed Method

MSR at 1, 4, 5

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

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer



▼ Arms and Interventions

Arms
Experimental: MSI Positive Colorectal Cancer

▼ Conditions

Conditions: MSI Positive Colorectal Cancer
MSI Negative Colorectal Cancer
MSI Positive Non-Colorectal Cancers

EX1005 at 1, 4, 5.

Pet. at 18-23; *see also* Reply at 21.

The MSR Provides a Reasonable Expectation of Success for the Second Step of the Claimed Method

MSR at 4, 5

Criteria: Inclusion Criteria:

1. Arm 1 only: Patients with MSI positive colorectal cancer
2. Arm 2 only: Patients with MSI negative colorectal cancer
3. Arm 3 only: Patients with MSI positive non-colorectal cancer

▼ **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


ClinicalTrials.gov archive

History of Changes for Study: NCT01876011

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

Study Record Versions

MERCK EX1002

EX1005 at 4, 5.

Pet. at 18-23; *see also* Reply at 21.

The POSA Was Motivated to Combine Pernot with the MSR to Carry Out the Claimed Method of Treatment

Alfred I. Neugut, M.D.



Medical Oncologist
Herbert Irving Comprehensive Cancer Center,
Columbia University

Merck Declarant Dr. Neugut ¶108

108. Pernot discusses treating MSI-H colorectal cancer. (*See generally*, EX1006.) The person of ordinary skill would, therefore, consider Pernot. The MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with pembrolizumab, an anti-PD-1 antibody (*supra* at §§ VI.B, VII.A.1), and Pernot concluded that those patients are "good candidates for immunotherapy." (EX1006 at 3741.) Immunotherapies include PD-1 inhibitors like pembrolizumab. (*See also* EX1029 at ¶ 82; EX1054 at 3; EX1011 at 141.) As such, the person of ordinary skill would have been motivated to combine Pernot's disclosure with the MSI-H Study Record's methods and carry out the clinical study that the MSI-H Study Record discusses.

EX1003 ¶108.

Pet. at 43.

The Prior Art Recommended Treating MSI-H Cancers with Immunotherapy

Alfred I. Neugut, M.D.



Medical Oncologist
Herbert Irving Comprehensive Cancer Center,
Columbia University

Merck Declarant Dr. Neugut ¶¶47-48

47. In view of this generally established scientific knowledge, by July 10, 2015, a number of references had also already specifically recommended that patients having cancers with the MSI-H biomarker should be treated with immunotherapeutic agents (in addition to the disclosures of the MSI-H Study Record). (EX1006 at 3740-41; EX1032 at e27817-5; EX1033 at 2968-69; EX1036

48. Independently, and mostly within a few months of each other, all of them arrived at the same proposed solution for improving the treatment of cancer: treating patients whose cancers have the MSI-H biomarker with immunotherapy. As discussed above, the reasons for those recommendations were grounded in well-established science. (*Supra* at ¶¶ 41-46.) Exemplary recommendations,

EX1003 ¶¶47-48.

Pet. at 10-11, 44-45.

MERCK EX1239

Pernot Recommended MSI-H Colorectal Cancers as "Good Candidates for Immunotherapy"

Pernot (April 2014) at 3741

> 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.

EX1006 (Pernot) at 3741.



Pet. at 10-11, 43; Reply at 21; EX1003 ¶¶48, 106.

MERCK EX1239

Pernot Discussed Promising Efficacy of PD-1 Inhibitors, Including Pembrolizumab

Pernot (April 2014) at 3738, 3742

Expression of these molecules, called "immune checkpoints", are important mechanisms of inhibition of antitumor immune response. 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[58-60].

toxicity induced by cetuximab. Finally, many immunotherapy strategies are being developed and tested in phase I to III clinical trials. The most promising strategies are boosting the immune system with cytokines, inhibition of immunoregulatory checkpoints, vaccina-



EX1006 (Pernot (April 2014)) at 3738, 3742; EX1150 ¶112.

Pet. at 43; *see also* Reply at 5, 22; EX1138 at 172:15-19.

Champiat Recommended Treatment of MSI-H Colorectal Cancer with PD-1 Inhibitors



Champiat (January 2014) at e27817-5

immune checkpoint blockers. Moreover, if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1and 2, early onset), all of which display severe genomic instability. Other tumors that

EX1032 (Champiat) e27817-5; EX1003 ¶¶43, 48.

Pet. at 10, 44; EX1003 ¶¶43, 47-48, 110.

Gatalica Encouraged Treating MSI-H Colorectal Cancer with Immunotherapy, Including PD-1 Inhibitors

Gatalica (November 2014) at 2965, 2968

Marked variations in PD-1/PD-L1 positivity have also been observed within general histologic types, but subtype analysis revealed significant correlations. For example, PD-1/PD-L1 were differently expressed in molecular subtypes of breast (TNBC vs. non-TNBC) and colon cancer (MSI-H vs. MSS cases) providing an indication for potential benefit of targeted immunotherapy in aggressive subtypes of breast and colon cancers for which no targeted therapy is currently available. We



EX1033 (Gatalica) at 2968.

Pet. at 10; EX1003 ¶¶47-48, 110.

Brown Recommended Treating Patients Having Tumors with Many Mutations and Infiltrated by Immune Cells with PD-1 Inhibitors

Brown (May 2014) at 743, 747

tumor immunoreactivity. Likewise, patients with tumors showing naturally immunogenic mutations and associated TIL are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies. There is evidence that such thera-

and *CTLA4*. Mutational epitopes were very scarce in tumors without evidence of CTL infiltration. These findings suggest that the abundance of predicted immunogenic mutations may be useful for identifying patients likely to benefit from checkpoint blockade and related immunotherapies.

EX1034 (Brown) at 743, 747.


Research

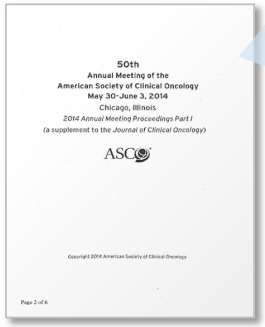
Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival

MERCK EX1034

Pet. at 10, 44; EX1003 ¶¶43, 44, 47, 48.

Llosa Concluded That Using PD-1 Inhibitors Could Enhance Clinical Benefit to MSI-H Colorectal Cancer Patients

Llosa (May 2014) at 243s


50th
Annual Meeting of the
American Society of Clinical Oncology
May 30-June 3, 2014
Chicago, Illinois
2014 Annual Meeting Proceedings Part I
(a supplement to the Journal of Clinical Oncology)
ASCO

3620 General Poster Session (Board #83), Sat, 8:00 AM-11:45 AM

Immune checkpoints expression in MSI versus MSS colorectal cancers and their potential therapeutic implications. *Presenting Author: Nicolas Jose Llosa, The Johns Hopkins University School of Medicine, Baltimore, MD*

Conclusions: The genetic origin of CRC dictates the nature and intensity of inflammation. A strong IFNg -driven inflammatory response in MSI CRC patients triggered the expression of PD-L1 and IDO-1 which could be targeted to enhance clinical benefit and be predictive of response to immune checkpoint inhibitors.

EX1039 (Llosa) at 243s.

Pet. at 44.

MERCK EX1239

Dr. Lonberg's Disregard of the Teachings of the Prior Art are Due to His Stated Belief a POSA Views the Art with a Skeptical Lens

JHU Declarant Dr. Lonberg at 86:18-87:2

Q Right. And from your perspective, a person of ordinary skill in the art would naturally have a skeptical lens when looking at a piece of prior art; is that fair?

A A person of ordinary skill in the art would have a skeptical lens when viewing any -- any scientific publication.

EX1138 (Dr. Lonberg Dep. Tr.) at 86:18-87:2.

Reply at 3-5; EX1150 ¶¶28-30.

MERCK EX1239

Ground 3: Obvious Over MSR, or MSR in View of Pernot, in View of Chapelle

Claims	Limitation
2 and 15	wherein the biological sample is a tumor tissue from the patient
8 and 21	wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample

Pet. at 46-49.

MERCK EX1239

Testing a Biological Sample of Tumor Tissue Was Known

Merck Declarant Dr. Neugut ¶115

115. Chapelle discusses testing to determine whether a tumor is MSI-H using the tumor tissue of a patient. (EX1007 at 3380, 3383.) Chapelle discusses a

EX1003 ¶115; *see also* EX1007 (Chapelle) at 3380, 3383.

JHU Declarant Dr. Lonberg at 50:9-18

Q The JHU-named inventors on the '393 Patent were not the first persons to test a biological sample to determine if a cancer patient is MSI-High, right?

A That's correct.

Q The JHU-named inventors on the '393 Patent did not invent testing a biological sample to determine if a cancer patient is MSI-High, right?

A That's correct.

EX1138 (Dr. Lonberg Dep. Tr.) at 50:9-18.

Not Contested by JHU

Pet. at 46-47; EX1003 ¶¶114-118.

MERCK EX1239

MSI-H Testing by Immunohistochemistry Was Known

Merck Declarant Dr. Neugut ¶115

115. Chapelle discusses testing to determine whether a tumor is MSI-H using the tumor tissue of a patient. (EX1007 at 3380, 3383.) Chapelle discusses a test to measure MSI by immunohistochemistry, and explains how, "[f]or practical purposes, [MSI-H] is equivalent to the loss of staining by immunohistochemistry (IHC) of one of the mismatch repair genes since both signify an abnormality in mismatch repair." (EX1007 at 3380.)

EX1003 ¶115; *see also* EX1007 (Chapelle) at 3380, 3383.

JHU Declarant Dr. Lonberg at 154:13-155:1, 155:8-10

Q Okay. And do you understand that the Chapelle paper, at the time it was published, explained to the public that an immunohistochemistry test was replacing MSI as a screening method for detecting MMR, right?

A Well, it was replacing the earlier PCR assay which looked at the size of the microsatellite repeat regions, and they're specifically amplified by PCR so that you can look at the size, using gel electrophoresis.

Q And the POSA would know that by the time of the July 10, 2015 critical date, right?

A That's correct.

EX1138 (Dr. Lonberg Dep. Tr.) at 154:13-155:1, 155:8-10.

Not Contested by JHU

Pet. at 48; EX1003 ¶¶115, 119-120.

MERCK EX1239

Ground 4: Obvious Over MSR, or MSR in View of Pernot, in View of Steinert

Claims	Limitation
3 and 16	wherein the biological sample is a body fluid from the patient

Pet. at 49-50.

MERCK EX1239

Testing a Biological Sample of Body Fluid Was Known

Merck Declarant Dr. Neugut ¶124

124. Steinert is directed towards the testing of circulating colorectal cancer tumor cells to determine how they survive and escape the immune system, including determining whether a tumor is MSI-H. (EX1008 at OF1.) Steinert further discusses determining whether a tumor is MSI-H using body fluid, specifically blood samples. (EX1008 at OF6.)

EX1003 ¶124; *see also* EX1008 (Steinert) at OF1, OF6.

JHU Declarant Dr. Lonberg at 47:19-48:5

Q And at the time of the critical date, July 10, 2015, you would agree that the person of ordinary skill in the art would know that to determine MSI-High status, tumor tissue or bodily fluid could be tested, right?

A Correct. The standard procedure is tumor tissue. Bodily fluid requires a more specialized assay.

EX1138 (Dr. Lonberg Dep. Tr.) at 47:19-48:5.

Not Contested by JHU

Pet. at 49-50; EX1003 ¶¶123-128.

MERCK EX1239

Ground 5: Obvious Over MSR, or MSR in View of Pernot, in View of Benson

Claims	Limitation
7 and 20	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
32, 34, 36, 38, 40, 42	wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy
29 and 30	wherein the colorectal cancer is metastatic colorectal cancer
37, 39, 41	wherein the colorectal cancer is metastatic colorectal cancer AND wherein the method results in specific claimed outcomes

Pet. at 50-57.

MERCK EX1239

Treating Metastatic CRC Patients After Prior Therapies Was Known

Merck Declarant Dr. Neugut ¶130

130. Benson discusses that, under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (EX1009 at 1034.)

EX1003 ¶130; *see also* EX1009 (Benson) at 1034.

JHU Declarant Dr. Lonberg at 179:1-5, 15-18

Q And you agree that the then NCC guidelines recommended including clinical studies as a therapy for metastatic cancer patients who had a third progression or more of their cancer, right?

***

Q "Yes" is the answer to my question?

A Yes. Regorafenib, if not given previously or clinical trial or best supportive care.

EX1138 (Dr. Lonberg Dep. Tr.) at 179:1-5, 15-18.

Not Contested by JHU

Pet. at 50-52; EX1003 ¶¶129-136.

MERCK EX1239

Ground 6: Obvious Over MSR, or MSR in View of Pernot, in View of Salipante

Claims	Limitation
9 and 22	wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample
10 and 23	wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample

Pet. at 58-60.

MERCK EX1239

MSI-H Testing by PCR or Next Generation Sequencing Was Known

Merck Declarant Dr. Neugut ¶152

152. Salipante discusses different tests to determine whether tumors are MSI-H. (EX1010.) Specifically, Salipante discusses two main types of direct tests to determine whether tumors are MSI-H: polymerase chain reaction ("PCR") (EX1010 at 1192) and next generation sequencing (EX1010 at 1192). Salipante discusses that "PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use." (EX1010 at 1192.) Salipante further explains that next generation sequencing, "allows MSI status [whether tumors are MSI-H or not] to be reliably deduced at the same time that other genes of interest are sequenced, without the need for dedicated inclusion of specific markers." (EX1010 at 1193.)

EX1003 ¶152; *see also* EX1010 (Salipante) at 1192.

Not Contested by JHU

JHU Declarant Dr. Lonberg at 48:16-22, 163:13-18

At the time of the critical date, July 10, 2015, you would agree that testing a patient for MSI-High status could be accomplished by carrying out a PCR test, right?

A Yes. "Could" is the critical part of that answer, yes.

Q Do you understand that Salipante explains that evaluating MSI phenotypes by next-generation sequencing is valuable?

A Yes. That's what is stated in the paper, and it's also what I think a person of ordinary skill in the art would have thought.

EX1138 (Dr. Lonberg Dep. Tr.) at 48:16-22, 163:13-18.

Pet. at 58-60; EX1003 ¶¶151-162.

Ground 7: Obvious Over MSR, or MSR in View of Pernot, in View of Hamid

Claims	Limitation
11, 12, 24, and 25	wherein the pembrolizumab is administered to the patient intravenously

Pet. at 61-63.

MERCK EX1239

Administering Pembrolizumab Intravenously Was Known

Merck Declarant Dr. Neugut ¶164

164. Hamid discusses that pembrolizumab was administered to cancer patients intravenously. (EX1011 at 134.) Hamid refers to pembrolizumab as "lambrolizumab" (EX1011 at 134), and the person of ordinary skill would have understood that lambrolizumab means pembrolizumab (EX1054 at 3 ("MK-3475 (pembrolizumab formerly lambrolizumab)."). Hamid demonstrated "a high rate of sustained tumor regression," when treating patients with advanced melanoma. (EX1011 at 134.)

EX1003 ¶164; *see also* EX1011 (Hamid) at 134.

JHU Declarant Dr. Lonberg at 179:19-180:6

Q Now, before the critical date, July 10, 2015, you would agree with me that pembrolizumab was administered to patients intravenously, right?

A Yes.

Q And before the critical date, you agree that there were publications that discuss intravenous administration of pembrolizumab, right?

A Yes.

EX1138 (Dr. Lonberg Dep. Tr.) at 179:19-180:6.

Not Contested by JHU

Pet. at 61-63; EX1003 ¶¶163-172.

MERCK EX1239

Ground 8: Obvious Over MSR, or MSR in View of Pernot, in View of Steinert and Hamid

Claims	Limitation
13 and 26	wherein the biological sample is a body fluid from the patient AND wherein the pembrolizumab is administered to the patient intravenously

Pet. at 63.

MERCK EX1239

Testing a Biological Sample of Body Fluid and Administering Pembrolizumab Intravenously Were Known

Merck Declarant Dr. Neugut ¶124

124. Steinert is directed towards the testing of circulating colorectal cancer tumor cells to determine how they survive and escape the immune system, including determining whether a tumor is MSI-H. (EX1008 at OF1.) Steinert further discusses determining whether a tumor is MSI-H using body fluid, specifically blood samples. (EX1008 at OF6.)

EX1003 ¶124; *see also* EX1008 (Steinert) at 1, 6.

164. Hamid discusses that pembrolizumab was administered to cancer patients intravenously. (EX1011 at 134.) Hamid refers to pembrolizumab as "lambrolizumab" (EX1011 at 134), and the person of ordinary skill would have understood that lambrolizumab means pembrolizumab (EX1054 at 3 ("MK-3475 (pembrolizumab formerly lambrolizumab)."). Hamid demonstrated "a high rate of sustained tumor regression," when treating patients with advanced melanoma. (EX1011 at 134.)

EX1003 ¶164; *see also* EX1011 (Hamid) at 134.

Not Contested by JHU

Pet. at 63.

MERCK EX1239

Disputed Issues

- "in response to" claim limitation and reasonable expectation of success to achieve the claimed two-step treatment method
- secondary considerations

JHU Cannot Meet Its Burden on Secondary Considerations

1. Blocking patents
2. Evidence **not** relevant as of the Critical Date
3. **No** nexus to any purportedly novel features of the claims

Reply at 4, 23-33.

MERCK EX1239

Purported Evidence Is Viewed from the Wrong Time Period

- Alleged rejection by BMS in **2012**

  EX1150 ¶182; *see also* POR at 74-75; EX2072 ¶¶183, 186, 189.

- Drugs available for the treatment of metastatic CRC in **2012**

  EX1150 ¶185; *see also* POR at 76-77; EX2090 ¶¶36-39, 42, 45.

- Alleged MSI-H Study funding decision in **2013**

  EX1150 ¶183; *see also* POR at 74-75; EX2072 ¶124, 138; EX2072 ¶124; EX2090 ¶55.

- Anecdotal named inventor comments **prior to 2013**

  EX1150 ¶183; *see also* POR at 73, 75, 81; EX2130 ¶¶26-27.

- Alleged disbelief in the MSI-H Study **prior to 2013**

  POR at 81, 84.

Reply at 4, 23-33.

MERCK EX1239

JHU and Its Declarants Ignore the State of the Art as of the Critical Date

- The MSR (June 2013) — EX1005
- Pernot (April 2014), Champiat (Jan. 2014), Gatalica (Nov. 2014), Brown (May 2014), Llosa (May 2014) — EX1006, EX1007, EX1032, EX1033, EX1034, EX1039
- Clinical study of another PD-1 inhibitor to treat MSI-H colorectal cancer patients — EX1053
- Additional Merck clinical study of pembrolizumab to treat MSI-H colorectal cancer patients — EX1148
- Prior successful treatment of MSI-H colorectal cancer patient with another PD-1 inhibitor — EX1038; EX1057

≠

Skepticism

Unexpected Results

Long-felt Need

(as of July 10, 2015)

Reply at 4, 23-33.

MERCK EX1239

JHU Cannot Establish Nexus

- No nexus between claimed method of treatment and Keytruda product
- No identification of unique characteristics of the claims
- No tie between alleged evidence and any purportedly novel features of the claims

Reply at 4, 23-33.

JHU Cannot Establish Nexus

Novartis at 1331

"In evaluating whether the requisite nexus exists, the identified objective indicia ***must be directed to what was not known in the prior art***—including patents and publications—which may well be the novel combination or arrangement of known individual elements."

Novartis AG v. Torrent Pharmaceuticals Ltd., 853 F.3d 1316, 1331 (Fed. Cir. 2017); *see also In re Huai-Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011).

Reply at 23.

MERCK EX1239

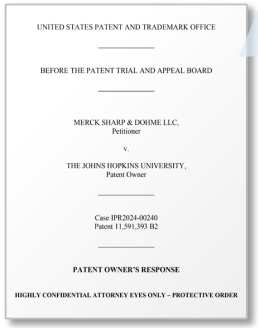
JHU Cannot Establish Nexus

- JHU relies on the claims as a whole, not any purportedly novel features of specific claims

POR at 66

invention." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). The merits of the claimed method of treatment relate to the claims ***as a whole***.

POR at 66.


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

Reply at 23, 27, 29-30.

MERCK EX1239

JHU Cannot Establish Nexus

- JHU does not tie any of the alleged secondary considerations evidence to purportedly novel features of specific claims

Purported Evidence Tied to:

Skepticism	• "Inventors' hypothesis" • MSI-H Study • Inherent results of the MSI-H Study POR at 73-76.
Long-felt Need	• Metastatic or advanced colorectal cancer POR at 76-80.
Unexpected Results	• Inherent results from MSI-H Study POR at 80-85.
Industry Praise	• Keytruda • Inherent results of the MSI-H Study POR at 68-73.
Commercial Success	• Keytruda POR at 86-91.

Reply at 4, 23-33.

MERCK EX1239

JHU's Alleged Evidence Should Be Afforded Little to No Weight

Skepticism

Long-Felt Unmet Need

Unexpected Results

Commercial Success

Industry Praise

Reply at 25-27.

MERCK EX1239

The Record Reflects a Lack of Skepticism by July 10, 2015

MSR at 1, 3

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

Submitted Date	Changes
June 10, 2013	None (earliest Version on record)

▼ Sponsor/Collaborators

Sponsor: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Responsible Party: Sponsor

Collaborators: Merck Sharp & Dohme LLC

EX1005 at 1, 3.



BMS Study Record at 1, 6

NIH U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT02060188

A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)

First Posted: February 11, 2014 [Estimate]

▼ Conditions

Conditions: MSI Positive Colorectal Cancer
MSI Negative Colorectal Cancer

EX1053 (BMS Study Record) at 1, 6.



Reply at 25-27; EX1150 ¶184.

MERCK EX1239

JHU's Allegations of Skepticism Are Contradicted by Its Declarant

JHU Declarant Dr. Lonberg at 225:15-21

Q And when the study record, and this is Exhibit 1005, was published on June 10, 2013, did you write to JHU expressing skepticism that the study was worth performing?

A No. In fact, I had already expressed enthusiasm to Drew Pardoll about doing such a clinical trial.

EX1138 (Dr. Lonberg Dep. Tr.) at 225:15-21.

Reply at 22, *see also* Reply at 25-27.

MERCK EX1239

JHU's Allegations of Skepticism Are Contradicted by Its Declarant

JHU POR at 73

697-98 (Fed. Cir. 1983). Here, neither the industry nor Merck believed in the inventors' hypothesis that MSI-H cancers would respond to pembrolizumab at a rate higher than MSI-stable cancers. EX1002, 205-206.

POR at 73.

JHU Declarant Dr. Pardoll at 121:5-12

Q So we're at exhibit page 205, and turning your attention to paragraph 22 of your Declaration, there you're not making any comments about something that Merck believed or didn't believe, right?

A That's right.

EX1140 (Dr. Pardoll Dep. Tr.) at 121:5-12; *see also id.* at 119:10-124:2.

Dr. Pardoll testified that his declaration provides ***no statement or testimony*** about what Merck or the industry believed or didn't believe

Reply at 26.

JHU's Allegations of Skepticism Are Contradicted by Its Declarant

JHU Declarant Dr. Le at 73:3-6, 73:16-74:7

A Okay. Again, they provided drug initially as listed here on this document, Collaborator. And then at some point later, they provided funding.

EX1139 (Dr. Le Dep. Tr.) at 73:3-6.

A Do I believe -- I believe I'm aware.

Q Okay. And it's your testimony and belief that Merck did not provide funding to support KEYNOTE-16 prior to 2015?

A I can't give you a date. I don't remember.

Q Is it your testimony that Merck did not provide funding to support KEYNOTE-16 prior to 2014?

A I can't remember the dates. I just can't remember. It's --

Q And is it your belief that Merck did not provide funding to support KEYNOTE-16 prior to February of 2014?

A I can't remember the dates.

EX1139 at 73:16-74:7.

Reply at 26-27.

MERCK EX1239

JHU's Allegations of Skepticism Are Contradicted by Its Declarants

JHU Declarant Dr. Lonberg at 228:19-20

Q And when you say that you're aware that Merck declined funding the trial, from where did you get that information?

A From Drew Pardoll.

EX1138 (Dr. Lonberg Dep. Tr.) at 228:19-22.

JHU Declarant Dr. Pardoll at 82:11-13

Q Did you tell Dr. Lonberg that Merck did not provide any funding for the study?

A I don't recall saying that.

EX1140 (Dr. Pardoll Dep. Tr.) at 82:11-13.

JHU Declarant Dr. Goldberg at 48:8-11, 48:14,112:1-4

Q Do you have any personal knowledge about whether Merck and JHU discussed funding of the 2013 MSI-high study while negotiating the contract covering it?

A I was not involved in those discussions.

* * *

Q You had no involvement in any discussions between JHU and Merck or JHU and BMS, correct?

A You asked me that question before and I said no.

EX1136 (Dr. Goldberg Dep. Tr.) at 48:8-11, 48:14, 112:1-4.

Reply at 26.

MERCK EX1239

JHU's Alleged Evidence Should Be Afforded Little to No Weight

Skepticism

Long-Felt Unmet Need

Unexpected Results

Commercial Success

Industry Praise

Reply at 27-29.

MERCK EX1239

The Record Reflects No Long-Felt Unmet Need by July 10, 2015

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶186

186. For example, Dr. Goldberg does not account for the fact that, as of July 10, 2015, (1) the MSI-H Study Record was in the prior art, (2) a number of other prior art references independently urged the POSA to consider treating MSI-H cancer with PD-1 inhibitors and PD-1 inhibitors, like pembrolizumab, were showing promise in treating tumors displaying certain characteristics that MSI-H tumors were known to display, and (3) a contemporary study of another anti-PD-1 inhibitor to treat patients with MSI-H colorectal cancer was ongoing. (EX2090 ¶¶28-64; *see also supra* §VII.C.1; EX1003 ¶¶33-49.) By ignoring the MSI-H Study Record and the other prior art known to the POSA as of July 10, 2015, Dr. Goldberg's analysis of an alleged long-felt unmet need focuses on the incorrect point in time and colorectal cancer more generally.

EX1150 ¶186.

Reply at 27-29.

JHU's Allegations of Long-Felt Need Are Contradicted by Its Declarant

JHU Declarant Dr. Goldberg at 81:17-20, 189:10-16

immunity to destroy cancer cells. And so companies all over the world began more aggressively researching immuno-oncology opportunities once the first breakthrough had occurred.

A As we discussed earlier in the paper by Dr. Ciombor and I, there was intense interest on the part of clinical oncologists, on the part of patients, and on the part of pharmaceutical companies of testing PD-1 inhibitors as quickly as possible to be sure that patients with cancer could realize their potential benefit.

EX1136 at 81:17-20, 189:10-16.

Reply at 28.

MERCK EX1239

JHU's Alleged Evidence Should Be Afforded Little to No Weight

Skepticism

Long-Felt Unmet Need

Unexpected Results

Commercial Success

Industry Praise

Reply at 24-25.

The Record Reflects Reasonable Expectation of Success for the Claimed Method of Treatment by July 10, 2015

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶184

(*See, e.g.*, EX2072, ¶¶187-89; EX2130, ¶¶28-31.) Instead, Dr. Lonberg and Dr. Le focus only on the ***degree*** of the results achieved in the MSI-H Study. (EX2072, ¶¶187-89; EX2130, ¶¶27-29.) In particular, as of July 10, 2015, the POSA would know that (1) the MSI-H Study was actually being conducted, and was therefore considered to have merit by Merck and JHU, as well as approval from the FDA and JHU's IRB (*see* EX1005; EX1116; EX1118-1119), (2) that BMS was conducting its own study of its anti-PD-1 drug in MSI-H colorectal cancer patients (EX1053), (3) that Merck had initiated an additional study evaluating pembrolizumab in MSI-H colon cancer (*see* EX1148), and (4) all of the teachings of the prior art literature discussed above in Sections VII.C-VII.J. Therefore, as of July 10, 2015, the POSA would not have found a positive outcome for the claimed methods of treatment unexpected.

EX1150 ¶184.

Reply at 24-25.

JHU's Alleged Evidence Should Be Afforded Little to No Weight

Skepticism

Long-Felt Unmet Need

Unexpected Results

Commercial Success

Industry Praise

Reply at 30-33.

Evidence of Commercial Success Is Weak Where Market Entry by Others Is Blocked

U.S. Patent No.	Filing Date	Date of Patent	Exhibit No.
8,354,509	June 13, 2008	January 15, 2013	EX1238
8,900,587	December 19, 2012	December 2, 2014	EX1214
9,220,776	September 30, 2013	December 29, 2015	EX1217
9,834,605	December 19, 2014	December 5, 2017	EX1215

Reply at 31; EX1151 ¶¶29-35.

JHU's Alleged Evidence of Commercial Success for the Claimed Method of Treatment Is Incomplete and Unreliable

Sean Sheridan, Ph.D.



Commercial Success Expert
VP of Intellectual Property
Charles River Associates

- Merck's blocking patents
  EX1151 ¶¶29-35.
- No consideration of what was known in the prior art
  EX1151 ¶¶40-42.
- Success due to unclaimed features
  EX1151 ¶¶36-39.
- Misleading patient and sales data
  EX1151 ¶¶45-71.

Reply at 30-33.

MERCK EX1239

JHU's Alleged Evidence Should Be Afforded Little to No Weight

Skepticism

Long-Felt Unmet Need

Unexpected Results

Commercial Success

Industry Praise

Reply at 29-30.

Keytruda's Approval to Treat MSI-H Colorectal Cancer Patients Is Attributable to the Intrinsic Properties of Merck's Drug

Paul E. Oberstein, M.D.



Medical Oncologist
Perlmutter Cancer Center
NYU Langone Health

Merck Declarant Dr. Oberstein ¶187

187. The approvals of Keytruda to treat patients with metastatic MSI-H cancer and metastatic MSI-H colorectal cancer are attributable to Merck's wonderful drug and are among the more than 40 approvals that Keytruda now has on its labeling, including at least 12 breakthrough therapy designation approvals (more than any other drug included in the Center for Drug Evaluation and Research (CDER) statistics). (EX1130; EX1134.) Indeed, as of July 10, 2015, the

EX1150 ¶187.

Reply at 29-30.

JHU's Purported Evidence of Industry Praise Is Not Linked to the Claimed Method of Treatment

- No link between claimed method of treatment and selection of abstract at ASCO

  POR at 68-70; EX2130 ¶¶42-46.

- No link between claimed method of treatment and FDA approval of Keytruda

  POR at 71-72; EX2130 ¶¶38-40, 52; EX2072 ¶184.

- No link between claimed method of treatment and FDA comments regarding Keytruda approval

  POR at 71-72; EX2130 ¶¶39, 52; EX2072 ¶¶182, 184.

- No link between claimed method of treatment and Merck's comments regarding JHU scientific work

  POR at 72-73; EX2130 ¶40.

Reply at 29-30.