

RECORD OF ORAL HEARING
U.S. PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARPE & DOHME LLC,
Petitioner
v.
THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

Case IPR 2024-00240 (Patent 11,591,393 B2)

Oral Hearing Held: March 31, 2025

Before DEBORAH KATZ, SHERIDAN K. SNEDDEN and
DEVON ZASTROW NEWMAN, Administrative Patent Judges.

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The above-entitled matter came on for hearing Monday, March 31, 2025, commencing at 1:00 p.m. EDT, at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia/via Video-conference.

P-R-O-C-E-E-D-I-N-G-S

1:50 p.m.

THE CLERK: All rise.

JUDGE KATZ: All right. Everyone, give us a few minutes
to -- okay. Okay. Judge Newman?

JUDGE NEWMAN: Yes. I'm here.

JUDGE KATZ: Okay. And the court reporter, are you ready?

THE COURT REPORTER: Yes, I am, Your Honor.

JUDGE KATZ: Okay. All right. Then let's begin. Good
afternoon. So we're here for oral arguments in IPR 2024 00240,
which pertains to the patentability challenges in the claims of U.S.
Patent 11,591,393. I am Judge Katz. This is Judge Snedden. And
Judge Newman is on the monitors appearing remotely. So, first, let
me find out who will be arguing for Petitioner?

MR. RATLIFF: Good afternoon, Your Honors. Preston Ratliff
on behalf of Petitioner. I will be arguing today along with my
colleague, Ms. Jessica Stauring.

JUDGE KATZ: Okay. Thank you.

MS. STAURING: Good afternoon, Your Honors.

JUDGE KATZ: Okay. And for Patent Owner, please.

MS. BROWN-MARSHALL: Good afternoon, Your Honors.
I'm Christina Brown-Marshall of Fish and Richardson, and I'll be
arguing on behalf of Patent Owners Johns Hopkins University. And I
will also have my co-counsel, Ms. Madelyn McCormick, who will
also be arguing today, too.

1 JUDGE KATZ: Okay. Thank you very much. All right. So a
2 few things before we get going. So just to remind everyone that
3 recordings of PTAB hearings is prohibited, and we do have a court
4 reporter here. So please speak directly into the microphones when
5 you're arguing. And please identify specific slide numbers and
6 numbering and figures, and any other pertinent information so that the
7 record is complete.

8 So the oral argument today is going to be open to the public and
9 streamed live. We haven't -- we understand that there is confidential
10 information in the record, but neither party requested that we close the
11 hearing room to maintain confidentiality. Is that correct? Was there a
12 request?

13 MS. BROWN-MARSHALL: No, Your Honor. I believe we
14 did make a request that that --

15 JUDGE KATZ: You did make a request?

16 MS. BROWN-MARSHALL: For a portion of the argument in
17 which there will be some confidential information discussed.

18 JUDGE KATZ: Okay.

19 MR. RATLIFF: Your Honors, on behalf of Petitioner, we
20 believe that the argument can remain open to the public. I think the
21 types of details don't need to be discussed openly. Your Honors
22 actually have the record and can refer to a slide. The disputes relate to
23 something different --

24 JUDGE KATZ: Okay.

25 MR. RATLIFF: -- on those issues.

1 JUDGE KATZ: But there was a request before, I just didn't
2 catch that. Okay. All right. So I think then we will provide for some
3 time probably at the end of the hearing for the portion that, I guess,
4 Patent Owner wishes to be confidential.

5 MS. BROWN-MARSHALL: Yes, Your Honor. So that would
6 be in the objective indicia section, and we were planning to address
7 that, I believe, towards the end of the hearing.

8 JUDGE KATZ: Right. We'll probably have to take some of
9 your time to set sort of a portion out at the end so that there can be a
10 response. You can present your position, and Petitioner can respond
11 without -- with the hearing room closed and the stream off.

12 MS. BROWN-MARSHALL: Okay. Yes, Your Honor.

13 JUDGE SNEDDEN: Do you agree with --

14 JUDGE KATZ: Yeah.

15 JUDGE SNEDDEN: -- your -- Petitioner counsel that details
16 we'll get in -- won't necessarily need to get into what -- exactly what is
17 considered confidential information, we could say at a higher level, or
18 are you requesting that we close the hearing room to all public access
19 and allow you to present your argument?

20 MS. BROWN-MARSHALL: So the slides that we will be
21 presenting have marked as confidential information on it. If Merck is
22 comfortable with us discussing those slides and information on the
23 slides in a public forum, then we have no issue with that.

24 MR. RATLIFF: And, Your Honor, we're not comfortable with
25 that. What we're saying, Your Honors, is that what's on the slide, the

1 details on those slides don't need to be discussed. They can be
2 discussed at a very, very high level. The record's before Your Honors.
3 The issues and these concerns, secondary considerations, largely go to
4 nexus and whether or not there's a tie. So that's something that could
5 be discussed in an open forum. And certainly Patent Owner can point
6 to the slide and say as you see here. But we don't think those details
7 need to be discussed, and this could proceed in an open forum.

8 JUDGE KATZ: So, yeah.

9 JUDGE SNEDDEN: I mean it seems like we have a conflict
10 here. You're saying you're going to present confidential information
11 on the screen, and they're basically asking you not to do that. So we'll
12 have to close the -- just you were requesting to close the hearing
13 room. Is that --

14 MS. BROWN-MARSHALL: Yes, Your Honor.

15 JUDGE SNEDDEN: Okay. And --

16 JUDGE KATZ: I mean I think we'll have a portion of the
17 hearing where we close --

18 JUDGE SNEDDEN: Yeah.

19 JUDGE KATZ: -- the room. So how -- well, okay. So we'll
20 talk about that in a moment, the actual mechanics of how that's going
21 to happen in a moment. Okay. All right.

22 MR. RATLIFF: Thank you, Your Honor.

23 JUDGE KATZ: Thank you, both.

24 MS. BROWN-MARSHALL: Thank you, Your Honor.

1 JUDGE KATZ: Okay. All right. So to that, each party will
2 have an hour and 45 minutes total because you both requested LEAP
3 arguments on top of the hour and a half that was authorized. So, I
4 guess, let's get into how much time do you think you need for the
5 portion that's --

6 MS. BROWN-MARSHALL: Your Honor, we would estimate
7 that 10 to 15 minutes is sufficient for us to present the slides that have
8 confidential information on them.

9 JUDGE KATZ: Okay. So that would take us to an hour and a
10 half for your argument that's open to the public?

11 MS. BROWN-MARSHALL: Yes, Your Honor. And, publicly,
12 I think we could probably do 10 minutes. We can do an hour and 20
13 minutes time

14 JUDGE KATZ: Okay. And how much would you like to
15 respond to the part that's closed?

16 MR. RATLIFF: Your Honors, we'd like to reserve -- this is the
17 portion that's closed?

18 JUDGE KATZ: Right. So this won't be your rebuttal. This
19 will be the portion -- this will be, I guess, your reply. Well, I guess
20 it'll be your rebuttal time that's closed. So we're going -- I guess the
21 way we're going to do this is that Petitioner will start. Patent Owner
22 will get a chance to present their argument. Petitioner will get some
23 rebuttal time. Patent Owner will get some rebuttal time. And then
24 we'll move into the closed portion of the proceeding. Does that seem
25 okay with my panel? So we'll have sort of two --

1 JUDGE SNEDDEN: Yeah.

2 JUDGE KATZ: -- little arguments going on, two sessions, an
3 open and a closed?

4 JUDGE SNEDDEN: Or you just close the last 10 minutes of
5 Patent Owner's opening argument, and then close the last 10 minutes
6 of the rebuttal period.

7 JUDGE KATZ: We can do that. Everybody will have to --

8 JUDGE SNEDDEN: Oh.

9 JUDGE KATZ: -- move in and out.

10 JUDGE SNEDDEN: Yeah.

11 MR. RATLIFF: Your Honors --

12 MS. BROWN-MARSHALL: Your Honor --

13 MR. RATLIFF: Just as a matter of procedure, I think we had --
14 whatever time is fine. If we had 90 minutes per side plus the LEAP
15 time.

16 JUDGE KATZ: Right.

17 MR. RATLIFF: So our plan was to reserve 30 minutes of that
18 for rebuttal. And so if in Patent Owner's portion, when they address
19 secondary considerations, if that's going to be 10 minutes in a closed
20 session, then we'll just use an equal amount of time to address that
21 because we're really not sure what they're going to say.

22 MS. BROWN-MARSHALL: Yeah. And, Your Honor, I was
23 going to suggest we could finish our presentation, the 10 minutes of
24 the closed hearing with confidential information. And then so we
25 don't have to close the courtroom twice, we could -- if Petitioners

1 would agree that they would start with their rebuttal while the
2 courtroom is still closed. And then once they finish with their rebuttal
3 time, then they could have the rest of their rebuttal be open. So we
4 only have to close the courtroom one way -- one time if we do it that
5 way.

6 JUDGE KATZ: I'm sorry. Can you repeat that?

7 MS. BROWN-MARSHALL: So if we, as Patent Owners, if we
8 present the confidential information -- if we reserve that for the last 10
9 minutes of our presentation so we close the hearing room for the last
10 10 minutes of our presentation.

11 JUDGE KATZ: Right.

12 MS. BROWN-MARSHALL: If Petitioner would agree that
13 they would start with their confidential rebuttal to that, then we could
14 just leave the courtroom closed for the first few minutes of their
15 presentation, then open the courtroom again. So we'd only have to
16 close the courtroom one time that way.

17 JUDGE KATZ: Petitioner, what do you think about that?

18 MR. RATLIFF: And, Your Honors, we'll -- if that makes
19 sense, we'll make that work.

20 JUDGE KATZ: Okay. That might be that -- okay. All right.
21 So why don't we go ahead with that. All right. So -- all right. So,
22 Petitioner, you would like to reserve -- whoops. You would like to
23 reserve 30 minutes for your rebuttal still. Is that correct?

24 MR. RATLIFF: That's correct, Your Honor.

1 JUDGE KATZ: Okay. Thank you. And, Patent Owner, I
2 know I usually ask this at the beginning of when you start arguing, but
3 how much time would you like to reserve for rebuttal in total?

4 MS. BROWN-MARSHALL: Five minutes.

5 JUDGE KATZ: Five minutes. Okay. Okay. All right. And,
6 excuse me, we just -- are we good?

7 JUDGE NEWMAN: I'm ready here.

8 JUDGE KATZ: You're ready, Judge Newman?

9 JUDGE NEWMAN: I am.

10 JUDGE KATZ: Yes. Okay. All right. Then I think I have an
11 idea how this will go. You will all help me with the logistics if it gets
12 confusing. But I think we're all on the same page. Okay. All right.
13 Thank you very much. All right. So why don't we get started? So,
14 Petitioner, whenever you would like to begin.

15 MR. RATLIFF: May I begin, Your Honors?

16 JUDGE KATZ: Please.

17 MR. RATLIFF: May it please the Board, this case concerns a
18 method of treating cancer that was posted publicly more than two
19 years before Patent Owner JHU reached back into the public domain,
20 and sought to patent that method as its own. Now since the Board's
21 institution decision, the record has grown substantially, and that's
22 largely because JHU has been lodging all sorts of arguments hoping
23 that something will stick, or distract from the fact that its patent
24 claims map directly back to the MSI-high study record, which is a
25 102(a) printed prior art publication.

1 Now for our presentation today, we plan to begin with the
2 challenged claims, and then we're going to get right to anticipation
3 and obviousness focusing on the disputed issues. My colleague,
4 Jessica Stauring, will address the secondary considerations arguments.
5 So with that, let's discuss the challenged claims. And let's turn to slide
6 6.

7 What we have here on the slide are the two independent claims,
8 and I want to point out some key facts about these claims. First, the
9 claims are simple. They're not complex. They're directed to a two-
10 step method for treating a colorectal cancer patient using Merck's drug
11 Pembrolizumab.

12 The first step we have here highlighted in yellow on the slide,
13 and that's just about testing a colorectal cancer patient to determine
14 that they're MSI-high. The second step is highlighted here in green,
15 and that's in response to determining that the colorectal cancer patient
16 is MSI-high giving them a therapeutically affective amount of
17 Pembrolizumab.

18 Second, the claims here are directed to treating a patient. Not
19 multiple patients. Not a group of patients. Not some patients that are
20 treated, and some patients that are not treated. They plainly say
21 treating a patient. And so that point's not missed, we underlined in the
22 slide the claim language where it refers to a patient because it's
23 important. It's important because to anticipate these claims, it just
24 requires a prior art disclosure of the same two-step method. And
25 that's what we have in the MSI-high study record, or MSR for short.

1 Now third, as the Board correctly observed in its institution
2 decision, when you look at the language of these claims, there's no
3 negative limitation inserted. The claims don't say only as a reaction
4 to -- as JHU wants the claims. It's just not there. It doesn't appear.
5 Now let's turn to slide 11 and get right to anticipation.

6 Your Honors, what we have here on slide 11 are the five main
7 disputed issues concerning anticipation. And the first one we have
8 here, we don't have to spend much time on it. This is JHU's argument
9 that the Board should apply an experimental use exception to negate a
10 printed publication as prior art. This makes no sense. The MSR is not
11 a use. It's a printed publication. And there's no case law that we are
12 aware of, and certainly no case law that JHU cited, that applies an
13 experimental use exception to negate the patentability bar created by a
14 102(a) printed publication.

15 And make no mistake, there's nothing out of the ordinary about
16 a ClinicalTrials.gov study record qualifying as prior art. We cited the
17 Board's Celltrion and the Federal Circuit's Salix decisions where a
18 ClinicalTrials.gov publication was relied upon for purposes of both
19 anticipation and obviousness. So JHU doesn't really have any
20 credible rebuttal here. Simply put, their argument has no support, and
21 what they're trying to do is turn on its head well-established law about
22 printed publications qualifying as prior art.

23 Now let's turn to slide 15, and we're going to discuss the second
24 disputed issue, which concerns the "in-response to" limitation. And
25 JHU's arguments here are basically the foundation for its entire case.

1 It's a clear example of JHU twisting facts and misleading in hopes of
2 avoiding anticipation. So let's turn to slide 16. JHU has three main
3 arguments, and they're shown here on the slide. And I'm going to
4 address each one of those thoroughly.

5 The first argument is that the Board's claim construction as the
6 institution state was erroneous. Well, that's not correct. The Board's
7 construction was correct, and I'll explain why. So let's turn to slide
8 17. What we see here on the slide we're showing portions of the
9 Board's institution decision where the Board acknowledged that there
10 was a causal relationship between the two claim steps.

11 Again, the first step is simply testing a colorectal cancer patient
12 to determine that they're MSI-high. And the second step in response
13 to that determination giving them an effective amount of drug. And
14 it's right here in the institution decision with the Board noting, and it's
15 on the slide, that Petitioner has sufficiently shown that there is a
16 reasonable likelihood of a causal relationship in the MSI-high study
17 record between treatment of colorectal cancer and determining their
18 MSI status.

19 So if the Board had omitted the causal relationship, which it
20 didn't, then the Board wouldn't be discussing the causal relationship
21 in the institution decision, and it wouldn't be doing an analysis of that
22 causal relationship in the MSR, which, of course, it did. We're
23 looking at it right here on the slide.

24 Now let's turn to the next slide, slide 18. Now the Board's
25 discussion on this point was thorough because it goes on at the

1 institution decision at pages 16 and 17, this is where these quotes
2 come from. And the Board is discussing the temporal relationship
3 between the two steps of the claim. Again, first step, determining that
4 the colorectal cancer patient is MSI-high, and the second, giving that
5 patient drug.

6 And as we see here on the slide, the Board is saying it does not
7 interpret the claim step as meaning anything other than treatment of
8 colorectal cancer patients after they have been determined to be MSI-
9 high. That is a recognition, as we understand it, that causality and the
10 temporal nature of the two steps of the claims go hand in hand. The
11 second steps is about giving Pembrolizumab after the status has been
12 determined, and that makes sense.

13 Now let's turn to slide 19, and Your Honors have seen in JHU's
14 papers, they write over and over again that the Board has omitted the
15 causal relationship in the claims. That's just not true. Even JHU's
16 declarant, Dr. Lonberg, when asked at deposition, he read the
17 institution decision, and he agreed that the Board had recognized the
18 causal relationship.

19 Now let's turn to slide 20 because I really want to explain what
20 is happening here. JHU is trying to insert a negative limitation into
21 the claim. What do they write? They express causal relationship
22 between these steps establishes that only CRC patients determined to
23 be MSI-high are treated. And the only there, it's bolded and italicized.
24 That didn't come from us. That came from JHU. But you know
25 what? That word only does not appear in the claims. We just went

1 through the claims. That's not there. So it's this negative limitation
2 that they're trying to add.

3 Now let's turn to slide 21, and this is back to the institution
4 decision at pages 17 and 18. And what we see, as we understand it, is
5 the Board's rejection of JHU's attempt to insert a negative limitation
6 into its claims. As the Board wrote, we do not interpret the in-
7 response-to claim limitation to mean that other patients are not
8 treated. That makes perfect sense. That's consistent with the plain
9 language of the claims.

10 Now I want to make Merck's position as to claim construction
11 absolutely clear. The Board's claim construction at the institution
12 stage was correct, and JHU misleads when it suggests that Merck has
13 been silent as to claim construction in this proceeding. So let's do
14 this. Let's do pull up JHU's demonstrative slide number 5. And we
15 will see what JHU says about this slide today, if they bring it up. But
16 it's misleading on many fronts.

17 The first thing, JHU is wrong in suggesting that Merck has been
18 silent as to claim construction. In the claimed construction section in
19 Merck's petition, at pages 11 and 12, we stated that given the
20 correlation between the MSR, the written description support for
21 JHU's patent, and the claims themselves, any reasonable claim
22 construction reads on the prior art. And, of course, that's true. If the
23 construction is the same construction as the Board set forth at the
24 institution stage, or if it's Merck's proposed construction in the District
25 Court, which was as the reaction specifically to.

1 JHU's claims read on the prior art. They read on the MSR. It's
2 also true, for what JHU apparently writes on this slide "in reaction to"
3 because that actually seemed very similar to what Merck proposed in
4 the District Court. But the problem is we know that there is a hidden
5 meaning in the construction that JHU is advocating for. For example,
6 if we turn to JHU's POR, and this is at page 8, let's take a look at that,
7 what we see, we see JHU saying in response to describes
8 administering the claimed treatment only as a reaction to. Only does
9 not appear in the claim language.

10 JUDGE KATZ: So, Mr. Ratliff, I see that only doesn't appear
11 there, but the reaction to part, if you -- I think their point is -- and
12 they'll correct me when they get a chance to argue, but that if you're
13 treating everybody, that's not a reaction to. That's just treating
14 everybody. Can you speak to that, that how is sort of -- you're going
15 to treat that patient if you try to keep it to that patient, you're going to
16 treat that patient regardless of whether they are MSI-H or not, and is
17 that in reaction to? I don't know if I'm even asking you a question, but
18 if you can respond to just --

19 MR. RATLIFF: Sure.

20 JUDGE KATZ: -- reflect please.

21 MR. RATLIFF: Sure. Sure. So this is how we can address it
22 because it is a negative limitation. And we can actually show how it
23 really doesn't make any sense. So if we turn, for example, to our slide
24 31, and this is what we're talking about, I think, is JHU's argument

1 that because the MSR discusses treating other cancers, it can't satisfy
2 the in-response-to claim limitation. I think that that's what it's about.

3 But this makes no sense because JHU's patent specification that
4 is the written description support, it discloses the same treatment
5 methods that are in the MSR, all three cohorts. And as a reminder,
6 there's only one clinical study here. One clinical study. That clinical
7 study is reported on in the MSR, and that clinical study is reported on
8 in JHU's patent specification.

9 Now -- and this goes more to the point because, amazingly,
10 JHU has been representing, and we see this in the slides to Your
11 Honors, that the patent specification discloses treating MSI cancers,
12 but not treating microsatellite stable cancers. And this is JHU slide 9,
13 and let's take a look at that. And this shows why JHU's claim
14 construction can't be correct.

15 Now what we're about to look at, it's beyond overzealous
16 advocacy. It's just entirely false. What JHU has done here on this
17 slide is that they put up a few quotes from the patent specification.
18 But if you look any deeper, even a tad deeper, it's easy to see how
19 misleading this is.

20 So, for example, if we focus our attention on the top right hand
21 portion of JHU's slide, and they take a snapshot of the specification
22 where it talks about design of the trial, and they cite this to say that the
23 specification only discloses treating MSI-high patients and not
24 microsatellite stable cancer patients.

1 But here's the issue. JHU shows Your Honors only lines 23
2 through 26 at column 13 omitting the very next line, the very next
3 sentence that undercuts JHU's argument. And let's bring that up. So
4 what do we see? The specification explains the trial design is for
5 three cohorts of patients to be administered 10 milligrams per
6 kilogram of drug every 14 days.

7 JUDGE SNEDDEN: Counsel, which slide are we looking at
8 right now?

9 MR. RATLIFF: So what we're looking at --

10 JUDGE SNEDDEN: Which slide number? Sorry? I'm having
11 --

12 MR. RATLIFF: Yes. So, Your Honor, we have on the left, we
13 have JHU slide number 9. And what we brought up on the right,
14 we've brought up the actual portion of the specification from the
15 patent.

16 JUDGE SNEDDEN: Thank you.

17 MR. RATLIFF: So we wanted to show the whole thing
18 because the context is important here. This is what JHU leaves out.
19 And what we see on the portion that JHU leaves out from the patent
20 specification, the very next sentence, it's discussing the three cohorts
21 that were treated, Cohorts A, B, and C. And that cohort B, that's the
22 microsatellite stable patients. It's right here.

23 So then if you look at lines 31 through 51 of column 13 of the
24 patent, it explains that the same treatment method and the same
25 outcome measures were evaluated for the MSI-positive and the MS

1 stable patients. So it's just not true that the specification does not
2 disclose treating MSI -- microsatellite stable patients. It discloses the
3 same treatment just like treating the MSR.

4 And, again, this is just a snapshot of what's misleading because
5 we're talking again about only one clinical study. The specification of
6 this patent reads just like the MSR. When you look at the figures, the
7 tables, the disclosures, they're all talking about these three treatments.
8 And this is the written description support.

9 JUDGE KATZ: So even if the specification discloses treating
10 all three, they could claim treating just one. Is that true? I mean they
11 don't have to claim treating all three even though the specification
12 discloses it?

13 MR. RATLIFF: That's correct, Your Honor. And that's exactly
14 what they did. They just claimed just treating one, treating a patient.
15 And that same method is disclosed in the MSR. It's just like the -- it
16 doesn't --

17 JUDGE KATZ: So it's the treating -- you're sort of dividing it
18 up as the treating just a patient, not as -- I guess your claim
19 construction then is that because the specification also says treating
20 patients who are not MSI-H, that they don't have written description
21 support for sort of excluding that from their claim?

22 MR. RATLIFF: It's not --

23 JUDGE KATZ: But --

24 MR. RATLIFF: -- in their claim.

25 JUDGE KATZ: Okay.

1 MR. RATLIFF: They have no language in the claim that
2 excludes treating other patients. There's no such negative limitation.
3 So it's absolutely a situation where the MSR is reading on the claims
4 because the MSR discloses, again, those simple two steps of the
5 method.

6 Now if we go back to slide 11, and then this is looking at the
7 disputed aspects of the claim limitations, and what I want to point out
8 in particular is -- I want to make another point about the in-response-
9 to limitation. And the point that I want to make here is that JHU said
10 a lot, and kind of went on in its surreply about these user intervention
11 cases. And it cites these in its surreply at pages 2 and 3.

12 Well, these are non-analogous cases. These cases deal with
13 Sofmer (phonetic), and automating technology, and there's like a user
14 in these particular cases that does something that triggers something
15 else. That's not this situation. This is a pharmaceutical patent, the
16 claims are far simpler, just a two-step method, treating. And then that
17 two-step method is about first determining that the colorectal cancer
18 patient is MSI-high, and then treating them in response.

19 Now I want to go to what we've talked about are the issues
20 relating to anticipation. And those are the first two issues on the slide
21 because -- and that's anticipation for all claims. There's certain claim
22 limitations that deal with an inherent disclosure of treatment results
23 that only apply to claims 31, 33, 35, 37, 39, and 41.

24 So let's take a -- let's take a look at those. And if we could turn
25 our attention to slide 34. And to help orient this analysis, if we turn to

1 slide 35, it helps clarify what we're talking about. So these dependent
2 claims are really directed --

3 JUDGE KATZ: So --

4 MR. RATLIFF: -- to natural --

5 JUDGE KATZ: I'm sorry. Sorry. Can I take you back for a
6 minute to -- just back to the claim construction?

7 MR. RATLIFF: Yes.

8 JUDGE KATZ: Is there anything in the MSR -- in the MS-H
9 report that does talk about the sort of timing of the treatment versus
10 the-- or that talks about the timing of the treatment versus the
11 determination? Or is there anything that you have that is support for
12 showing that the determination was either before the treatment, or
13 after the treatment, or some other time? Do you have any evidence
14 about that?

15 MR. RATLIFF: We do, Your Honor. So if we take a look at --
16 let's go to slide 22, and we're orienting ourselves with slide 22, this
17 concerns the MSR. And as we know -- and just for clarification, the
18 MSR, this was posted more than two years before, and it includes the
19 two treatment method steps that I'm going to show Your Honors.

20 So if we turn to slide 24, this is taking a step back and looking
21 at the disclosures of the MSR. And here in slide 24, it's teaching that
22 a patient's MSI-high status is determined first. It has to be because
23 when you look at the -- what you see in the MSR here in the
24 disclosures, you have the focus of the study being for microsatellite-
25 unstable tumor type patients.

1 Then it gives inclusion criteria for the various arms. And for
2 arm 1, it has to be positive -- MSI-high positive colorectal cancer
3 patients. You couldn't put them in the arms. You just don't give drug
4 first. And our -- for example, our declarant explains this, Dr.
5 Oberstein. And this is on slide 25.

6 And what he's explaining is that when it has these disclosures,
7 it's only logical that you test a colorectal cancer patient to determine
8 their MSI-high status first. And he also explains that this this is not a
9 randomized trial because if it was a randomized trial, then you could
10 do it, you know, a different way. But in that disclosure, for example,
11 is on slide 29, the study design is this allocation where it's not a
12 randomized trial.

13 And if we go back to slide 28, and this addresses really the
14 argument that's coming from JHU, which is an illogical argument that
15 this was some sort of all-comers design. But, again, that's ignoring
16 the reality. When you look at the study record, it has particular arms
17 that you have to designate colorectal cancer patients.

18 And it ignores the reality and the perspective that the person of
19 ordinary skill would understand that for MSI-high colorectal cancer
20 patients, and Dr. Oberstein talks about this, and it's reflected on slide
21 28, is that there is a low incidence of those particular cancer patients.
22 Only 15 percent of the population. And it's lower when you're dealing
23 with patients that are in the metastatic setting.

24 And that's what we're talking about here for this particular type
25 of -- for this particular type of treatment. So it would be illogical to

1 give drug to patients, and then later try to put them in arms. You
2 wouldn't even know if you have enough patients to fulfill the study
3 arm. So the MSR does treat it.

4 JUDGE KATZ: And that's -- Dr. Oberstein's testimony is your
5 support for the timing?

6 MR. RATLIFF: It's Dr. Oberstein's testimony. It's also, if we
7 look at slide 27, we think it's right here in the MSR, this teaching the
8 POSA. The --

9 JUDGE KATZ: So inclusion criteria couldn't be just those
10 three types of people are included in the study, and then they're put in
11 the arms later? Inclusion means that they're put in the arms first, and
12 then they're treated?

13 MR. RATLIFF: Yes.

14 JUDGE KATZ: Okay.

15 MR. RATLIFF: Yes.

16 JUDGE KATZ: Because all we have here is just the word
17 inclusion criteria. But that implies -- and it's supported by, I guess,
18 you're saying Dr. Oberstein's testimony that that's what inclusion
19 criteria means?

20 MR. RATLIFF: Yes. We think it's supported by Dr.
21 Oberstein's testimony. We think it's also supported by what's actually
22 shown in the MSR when you look at the disclosures. For example,
23 just looking even at --

24 JUDGE KATZ: I mean it doesn't say determine first, and then
25 treat. The MSR study doesn't actually say those words.

1 MR. RATLIFF: It doesn't use those words, Your Honor.

2 JUDGE KATZ: Okay.

3 MR. RATLIFF: But when you look at it, and when we look at,
4 for example, slide 27, that's the perspective that the POSA has.

5 JUDGE KATZ: Okay.

6 MR. RATLIFF: The study is about treating a certain type of
7 patients. You want to test them. That's the instruction. It's such an
8 evident thing to the POSA that this is the way that you proceed. We
9 think -- doesn't have to use those specific words. And to be placed in
10 that arm, and to be treated, you have to be tested.

11 Now with that, if we go back to slide 11 -- and I'm happy to
12 address any questions that Your Honors may have about the in-
13 response-to limitation. But slide 11 helps orient us, again, about the
14 other claim limitations that are read on by the MSR. And, for
15 example, the inherent disclosure of treatment results, we were talking
16 about those claims. And if we go to slide 34, and then those claims
17 are discussed on slides 35 and 36. It's just showing what those claims
18 are about. It's directed to the natural results that flow from carrying
19 out the claim two-step method.

20 Now what we have is a situation where JHU is arguing for
21 patentability based upon the actual inherent results. But that's just not
22 the law. So if you turn to slide 37, we know that the Federal Circuit in
23 the Schering case made plain that an alleged invention is in the public
24 domain if it is the natural result flowing from the explicit disclosures
25 of the prior art.

1 Now in Schering, it was a metabolite that did not exist. It
2 wasn't known. But there was a prior art method disclosing a method
3 of treating by administering the drug Loratadine, and that would
4 naturally produce the metabolite. So the result? Inherent anticipation.

5 And if you turn to slide 38, there, the Federal Circuit in re
6 Montgomery case, it was a planned clinical study that had not --
7 where the results had not been disclosed. So no results known at the
8 time. And applying the Schering principles, the Federal Circuit found
9 anticipation, and made plain that even if the claims include an efficacy
10 request, efficacy is inherent in carrying out the claim steps.

11 And now JHU, they double down on their surreply claiming
12 that the Montgomery case is distinguishable saying that the MSR is an
13 invitation to investigate. But as an initial matter, this invitation to
14 investigate language, that's something that came from the dissent in
15 the in re Montgomery case. It's just a policy argument supported by a
16 dissent. And the majority in the Montgomery decision, they explain
17 that the Hope Study that was involved in the Montgomery case was
18 far from an abstract theory.

19 Similarly, the MSR is far from some sort of abstract theory. It's
20 not an invitation to investigate. It's a phase II clinical study involving
21 a known cancer drug, and that known cancer drug was showing
22 efficacy in cancer patients. And that's in the Hamid publication,
23 Exhibit 1011.

24 The dose disclosed to treat patients in the MSR was published
25 and known. The MSR, as we talked about, disclosed the two-step

1 method: Testing an MSI-high colorectal cancer patient to determine
2 that they were, in fact, MSI-high, and then administering drug. The
3 MSR sets out both the inclusion and exclusion criteria for the patients
4 to be treated. Plus at Pages 4 and 6 of the MSR it details and sets out
5 the very specific outcome measures that are to be computed as the
6 result of the study.

7 There's nothing about this that's abstract. They MSR had -- also
8 had a recognized rationale, and that was all based upon publicly
9 known documents. And we know that from JHU's IND submission
10 where it explains this rationale, and that's Exhibit 1116 at 2, 18
11 through 19, and 39 through 40.

12 So we have to remember this other point that this is not a
13 treatment method for some -- that this is treatment method for
14 critically ill cancer patients. If it were some sort of abstract theory,
15 then the FDA would not be allowing the publishing of the MSR and
16 conducting the study that flowed from it.

17 And we also have to remember and not forget that the posting
18 of the MSR, part of the reason for that posting is it was intended to
19 inform the public including critically ill cancer patients and their
20 doctors about a treatment method that could potentially help them.
21 This is a far cry from an abstract theory.

22 And while you may hear JHU say otherwise, but Merck wasn't
23 skeptical of the study. Merck agreed to do the study in collaboration
24 with JHU. Merck gave its drug free as part of the study. It was a
25 collaborator. And it also helped to set the dose for the study.

1 Now there's another point we want to make is that JHU hasn't
2 made any assertions about the lack of enablement of the MSR
3 because, again, it's a simple two-step treatment method that's laid out
4 in the MSR.

5 And, finally, per the federal Circuit's decision in Schering, if we
6 took JHU's patent claims and went back in time before the MSR
7 published, JHU would be able to assert infringement if someone
8 followed the steps of the method disclosed in the MSR because it's the
9 sole embodiment of written description support for their claims. But
10 the reality is the other way around with the MSR being published
11 more than two years before JHU's alleged invention date of July 10,
12 2015. So Schering makes plain that JHU's alleged invention is
13 unpatentable.

14 Now I want to turn to slide 41 and address another disputed
15 issue, and this only applies to certain claims. And if we turn to slide
16 42, it's clear what we're talking about. So there's certain dependent
17 claims that point out that the patient had a different cancer therapy
18 before, and that their cancer progressed. And so I want to walk
19 through this because JHU's argument ignores the plain teachings in
20 the MSR and the perspective that the POSA would understand at the
21 time.

22 So let's turn to slide 43, and so what we have here on slide 43,
23 and again, this is just a snapshot from the MSR, but it's where it's
24 talking about the exclusion criteria. So the MSR is recognizing that
25 its treatment methods, and they're telling the POSA is appropriate for

1 critically ill cancer patients, people that have already received a prior
2 treatment. And recognizing that it's calling out certain treatments that
3 if you already had these type of treatments, for example, an anti-PD1
4 inhibitor like Pembrolizumab, then you wouldn't be appropriate for
5 the study.

6 And so what we have here on the slide, and it's highlighted
7 there in yellow, this exclusion criteria. This is a clear teaching. If we
8 turn to slide 44, we also know from the standard of care at the time,
9 and this was set out in the National Comprehensive Cancer Network
10 guidelines, that to do a clinical study of this type, you couldn't be a
11 naïve patient. You had to have a prior treatment. And that's shown
12 here on this slide. There's initial therapy, and then your cancer has
13 actually progressed after that therapy. Clinical trials only show up
14 here after the second progression.

15 So that's the perspective that we have. And it's part of the
16 continuum of care for a cancer patient that a POSA would understand.
17 And if we turn to slide 45, Merck's declarant, Dr. Neugut, testified
18 about this testifying about the cancer guidelines as summarized in the
19 Benson reference, and discussed that this is the standard for critically
20 ill, advanced stage cancer patients. You generally have to have
21 received at least two prior therapies, and this claim's only talking
22 about one.

23 Now if we turn to slide 46, this is the situation where Dr.
24 Oberstein is responding to JHU's declarant Dr. Lonberg who is really
25 disregarding the context of the MSR. The MSR can't be looked at or

1 understood in isolation. It has to be understood in the context of the
2 prior art. And, again, as Dr. Oberstein mentions, that you have to
3 have a measurable advanced disease. And to be measurable, that
4 means that you had a prior cancer therapy, and then your cancer
5 progressed. That's how you're measuring. So that's what we're
6 talking about.

7 Now I want to turn to slide 47, and this concerns the last
8 disputed issue as to anticipation. And if we turn to slide 48, it clarifies
9 what's at issue. There are two dependent claims that specify that the
10 colorectal cancer patient is a metastatic colorectal cancer patient. And
11 the arguments here, if we turn to slide 49, as to why these claim
12 limitations are met by the MSR, are similar to what we just discussed
13 because we're dealing with critically ill cancer patients in their
14 advanced stages.

15 And so we see, if we turn to the next slide, which is slide 50,
16 we see here again those cancer guidelines for colorectal cancer
17 patients. And at the top, it's talking about continuum of care,
18 chemotherapy for advanced or metastatic disease. That's exactly what
19 we're talking about. And clinical trials is only appropriate in those
20 advanced stages. So that's the background and perspective that we
21 have for these particular claim limitations. And Dr. Neugut, on slide
22 51, we explain that he talks about how the patients, and we only need
23 a patient, has metastatic colorectal cancer, and is an advanced-stage
24 cancer.

1 Now I want to turn back to slide 11 because these last two
2 points that we looked at concerning disclosure of prior cancer therapy
3 and treating a metastatic colorectal cancer patient, we believe that
4 they're absolutely taught by the MSR. And they are informed by the
5 perspective of the POSA in the state of the art. But we also have
6 obviousness arguments related to them.

7 So even if Your Honors didn't believe that they were
8 anticipated, they're obvious by the prior art. And JHU doesn't have
9 any independent arguments that rebut that. They don't make any
10 claim whatsoever, so that stands uncontested. So with that, I'd like to
11 turn to the issue of obviousness unless Your Honors have any
12 particular questions about the anticipation issues.

13 JUDGE KATZ: I'm okay. Judge --

14 MR. RATLIFF: So turning to slide 54, so as initial matter, we
15 don't think there's any reason why the Board should even reach the
16 issues of obviousness as to the independent claims given the prior art
17 disclosures of the MSR. But if the Board disagrees -- well, let me put
18 it this way, if the Board agrees with us, because we're going to address
19 uncontested issues first, then -- and the anticipation of the independent
20 claims, then all the dependent claims are rendered obvious because
21 JHU doesn't have any separate contest.

22 We see that here in the slide. They don't say things such as
23 testing biological fluid is not rendered obvious by the claims. They
24 don't say things such as a metastatic cancer patient is not rendered

1 obvious. So that's really important. And with that, let's turn to slide
2 55, and discuss the disputed issues.

3 Now the first issue here is what we really have been discussing
4 in the context of anticipation. It's the end response to claim limitation
5 and reasonable expectation of success to achieve the claimed two-step
6 method. These things go hand in hand. And, again, this is just a two-
7 step treatment method of first determining that the colorectal cancer
8 patient is MSI-high, and then second, giving them the drug.

9 And to be clear here, the reasonable expectation of success is
10 about carrying out the method. Can you test the colorectal cancer
11 patient to determine that they're MSI-high? And then second, can you
12 give them an effective amount of Pembrolizumab? Of course you
13 can. The MSR says that. And the other documents provide additional
14 motivation for support such as the Pernot reference.

15 But let's turn to slide 57 because the analysis here, it really is
16 straight forward. The MSR disclosed the two-step treatment method
17 and our various prior art references that we rely upon, they urge a
18 POSA to carry out that simple two-step method that we see in the
19 MSR.

20 And, now, we don't think there are any gaps that are missing in
21 the MSR. But even if they were, as we explain in our petition, and
22 this is at Page 43, for example, the combination of the MSR and
23 Pernot would fill any of those gaps because Pernot, for example,
24 teaches that colorectal cancer patients are good candidates for
25 immunotherapy. So it's just encouragement to carry out the steps of

1 the MSR. And this was an argument that we understood that the
2 Board noted in its institution decision at page 23.

3 And so to be even more clear because JHU, we expect them to
4 make an argument regarding what we do rely upon. JHU says that
5 Merck doesn't rely upon Pernot or any other prior art for the in-
6 response-to limitation.

7 Well, that's really not correct because in the context of
8 obviousness, what we rely upon is the combination of the MSR in all
9 the references, reference after reference urging a POSA to carry out
10 the method of treatment in the MSR all saying that colorectal cancer
11 patients, particularly MSI-high patients, are good candidates for
12 immunotherapy. So you can't separate the two. It's not about whether
13 Pernot does it alone. The idea is that -- and what we understand, is
14 that it's the combination of looking at those references. And we talk
15 about that in our petition at, for example, Page 44.

16 Now I want to turn to slide 62 because slide 62, and this is the
17 beginning portions where we talk about how Dr. Neugut explains how
18 the POSA was motivated to combine Pernot with the MSR to carry
19 out the claim method. Again, with Pernot pronouncing that
20 immunotherapy in MSI colorectal patients are good candidates for
21 immunotherapy. Everything here is about encouragement. We
22 haven't seen a prior art reference saying this is not going to work.
23 Don't do it. Be careful. Be cautious. That doesn't exist.

24 And if we look, for example, and turn to slide 66, and this is the
25 Champiat publication that we rely upon, what do we see? Again,

1 more prior art recommending treatment of MSI-high colorectal cancer
2 patients with PD-1 inhibitors. It's right there. And if we turn to slide
3 67, the Gatalica prior art reference that we rely upon, that also
4 encourages treatment of MSI-high colorectal cancer patients with
5 immunotherapy including PD-1 inhibitors. This is the body of
6 information that the POSA has as of the alleged July 10, 2015
7 invention date. The MSR in reference after reference encouraging the
8 POSA to carry out the steps of the MSR.

9 JUDGE KATZ: So those other references, Pernot is the only
10 one in your challenge, in your ground 2, right?

11 MR. RATLIFF: Pernot is the only one in ground 2. Yes.
12 That's correct.

13 JUDGE KATZ: And then there are these other references
14 which you're saying -- how do they fit in?

15 MR. RATLIFF: The other references fit in because they're the
16 background knowledge of the prior art. They all --

17 JUDGE KATZ: Okay.

18 MR. RATLIFF: They all go to show the encouragement. So
19 Pernot is -- yes, Your Honor, it's the main reference we're relying
20 upon for ground 2.

21 JUDGE KATZ: And Pernot is pretty broad. I mean
22 immunotherapy is pretty -- is a very broad statement that it's a good
23 candidate for immunotherapy. That could be a lot of different things,
24 right?

1 MR. RATLIFF: It could be a lot of different things, but Pernot,
2 for example, it talks specifically about PD-1 inhibitors. There's a
3 citation in Pernot, I believe it's reference number 50, to the Hamid
4 publication which discloses Pembrolizumab. And in that Hamid
5 publication, it talked about dosing Pembrolizumab at the same dose
6 that's in the MSR, and it also is talking about Pembrolizumab showing
7 efficacy for melanoma. So the Pernot provides --

8 JUDGE KATZ: And elsewhere in Pernot than just that one
9 sentence?

10 MR. RATLIFF: Yes. That's right. Because --

11 JUDGE KATZ: And then you're also saying that this is in
12 combination with the MSR?

13 MR. RATLIFF: That's correct, Your Honor.

14 JUDGE KATZ: Okay.

15 MR. RATLIFF: Yes. There are many disclosures. And, for
16 example, we have a slide on this. This is slide 65, and this is a
17 reference to what's found in Pernot. And so this is beyond the
18 statement which we do think is very important that MSI-high patients
19 are good candidates for immunotherapy. This is Pernot actually
20 talking about these PD-1 therapies, and showing that -- and explaining
21 that they're showing promise. And we look here 58 -- I believe I
22 misspoke, so I think it's reference number 60 is what the -- is the
23 Hamid publication.

24 JUDGE KATZ: Mm-hmm.

1 MR. RATLIFF: And that's shown right here. So, yes, there is
2 disclosures beyond that. And, Your Honors, as part of the other art, as
3 part of the other background art that we rely upon, and that is the
4 perspective of the POSA, we can look at slide 68, and this is Brown.
5 And Brown recommending treating patients having tumors with many
6 mutations, and that's what these MSI-high patients are. And treating
7 that with PD-1 inhibitors like Pembrolizumab. Slide 69, the Llosa
8 publication concluded that PD-1 inhibitors could enhance clinical
9 benefit to MSI-high colorectal cancer patients. It's right here before
10 us.

11 And what we're talking about here is a reasonable expectation
12 of success in carrying out the treatment method of the MSR. Those
13 two steps. The prior art here is urging that. And we're just looking
14 here, and we see this. This is far more than the preponderance of the
15 evidence. But that's what the art is teaching. We haven't seen art
16 saying that this is not going to work.

17 So with that, if we turn to slide 71. Slides 71 through 83, Your
18 Honors, we include these mainly for completeness because they
19 address our other challenged grounds, and these are grounds that deal
20 with dependent claims where JHU has not contested. For example,
21 the claims talk about testing biological -- talk about testing a
22 biological sample. And some of those dependent claims say, well,
23 that could be body fluid. Well, they don't have any independent
24 argument about the prior art not disclosing that combination, for
25 example.

1 And so that's what you see throughout slides 71 through 83
2 because what JHU is really doing is basically putting all of its eggs as
3 to obviousness in this basket of the in-response-to claim limitation and
4 a reasonable expectation of success. And, of course, they do talk
5 about secondary considerations, which my colleague Ms. Stauring
6 will address.

7 So with that, I'd like to turn it over to my colleague, unless
8 Your Honors have any questions about the issues of obviousness.

9 JUDGE KATZ: I'm good. Judge Newman? Okay. Thank
10 you.

11 MR. RATLIFF: Thank you.

12 JUDGE KATZ: You got around about 25 minutes left.

13 MS. STAURING: May it please the Board. Your Honors, for
14 any claims that you find anticipated here for the reasons explained by
15 my colleague, Mr. Ratliff, secondary considerations are irrelevant to
16 the Board's outcome as it pertains to those claims.

17 I'll address secondary considerations and talk about the weight
18 that the Board should afford to secondary considerations here, and
19 then I'll come back on rebuttal and address JHU's arguments and the
20 additional weaknesses of its evidence in more detail given that JHU
21 has the burden on -- the initial burden on secondary considerations.

22 There are three independent reasons here, Your Honor, that
23 secondary considerations should carry very little, if any, weight in the
24 Board's analysis. First, the existence of blocking patents in the record

1 here reduces the weight of secondary considerations. We can turn to
2 slide 104 please.

3 There is no dispute that Pembrolizumab is Merck's drug. And
4 on Merck's website, Merck identifies for the public certain patents
5 associated with its drug product and its uses broadly in the treatment
6 of cancer. Those patents that I'm showing -- some of those patents
7 that I'm showing here on slide 104, all issued or were filed prior to the
8 alleged invention date here, and are in the record. And under the
9 Federal Circuit's precedent, these patents reduce the weight of
10 secondary considerations alleged by JHU here like commercial
11 success, and long felt, unmet need, for example.

12 There is no dispute here that these patents are associated with
13 the Keytruda drug product, and its uses broadly in the treatment of
14 cancer. And they were discussed by Merck's commercial success
15 expert, Dr. Sean Sheridan in his declaration where he discussed the
16 preventative effect that these patents would have on others to develop
17 methods of treatment using Merck's drug. And under the Federal
18 Circuit's precedent, these patents reduce the weight of secondary
19 considerations here. We can turn back to slide 85 please.

20 To my second point, JHU's alleged evidence here is polled from
21 a time period that's more than two years before the alleged invention
22 date here. And this lack of temporal relevance between the alleged
23 evidence of secondary considerations and the alleged invention date
24 reduces the weight that that evidence should carry because during
25 those intervening years, three important things happened.

1 First, the method of treatment published in the MSR in June of
2 2013. Second, the additional references discussed by my colleague,
3 Mr. Ratliff, encouraged the treatment described by the MSR. And
4 third, additional studies to treat MSI-high colorectal cancer patients
5 with Pembrolizumab and with another PD-1 inhibitor published prior
6 to the alleged invention date here.

7 And so this focus on this purported evidence from a time period
8 in 2012 and 2013 effectively asks the Board to attribute weight to that
9 evidence that does not have the benefit of the state of the art that
10 existed as of July 10th, 2015. And so the Board should afford very
11 little, if any, weight to that evidence to the extent it does credit JHU's
12 evidence. And so --

13 JUDGE NEWMAN: So this is Judge Newman. What is the --
14 what is the time period that you suggest we should be looking at?

15 MS. STAURING: Your Honor, we suggest that Your Honors
16 assess the question of obviousness as of the alleged invention date,
17 which is here is July 10th, 2015. And the state of the art that existed
18 as of that date. And JHU's focus on purported evidence from 2012
19 and 2013, therefore, request that Your Honors disregard all of the
20 evidence that's in the record here that existed to reflect the state of the
21 art as of that date.

22 JUDGE NEWMAN: But can't we just consider all the evidence
23 together?

24 MS. STAURING: Yes, Your Honor.

1 JUDGE NEWMAN: But why do we need to disregard the
2 earlier evidence --

3 MS. STAURING: Your Honor --

4 JUDGE NEWMAN: -- in your opinion?

5 MS. STAURING: Sorry. Our argument is a little bit different.
6 It's not that Your Honors should entirely disregard that evidence. Our
7 argument is that that evidence should carry very little, if any, weight
8 in the Board's analysis of obviousness in its totality based on the
9 evidence in the record put forth by Petitioners as well as Patent
10 Owner.

11 JUDGE NEWMAN: I understand. Thank you.

12 MS. STAURING: And third, Your Honors, there is no nexus
13 here between the alleged secondary considerations and the patent
14 claims of the 393 patent. In its Patent Owner response, and likely
15 here today, JHU argues for either a presumption of nexus, or nexus in
16 fact.

17 With respect to the presumption of nexus, however, the law is
18 clear that a presumption of nexus only exists when evidence is tied to
19 a specific product, and that product is coextensive with the patent
20 claims. There is no question here that the 393 patent is not a product
21 patent. It does not have claims that are directed to the Keytruda
22 product itself. So under the law that's cited by JHU in its Patent
23 Owner response, a presumption of nexus here is not warranted. And
24 JHU has not met its burden to establish one.

1 With respect to nexus in fact, JHU's arguments similarly fail
2 because it's fundamental for nexus to exist that the secondary
3 considerations be tied to features of the patent claims that are not
4 already known in the prior art. JHU does not make any attempt in its
5 patent owner response to tie its alleged evidence to purportedly novel
6 features of its patent claims, nor could it because the treatment method
7 that's claimed here was known in the prior art as was the drug itself.
8 Without any nexus, the alleged evidence of secondary considerations
9 here should carry very little weight in the Board's determination of the
10 obviousness of the patent claims.

11 In addition to these three important points, there is one other
12 thing that we ask Your Honors to please keep in mind when JHU
13 presents on secondary considerations today. JHU may show Your
14 Honors a timeline slide. That's JHU slide 89. And if so, JHU will
15 likely allege that that slide represents the evidence of secondary
16 considerations in this case. And when Your Honors see that slide, we
17 ask that you please keep in mind what we're showing on the slide here
18 on slide -- Petitioner's slide 87 because this evidence reflects the state
19 of the art as of the alleged invention date, and much of this evidence
20 will be omitted from JHU's timeline slide.

21 Unless there are any questions, I'd like to reserve the remainder
22 of the time for rebuttal where I'll come back and address JHU's
23 arguments today as well as the specific weaknesses with its five
24 alleged secondary considerations here. Thank you, Your Honors.

25 JUDGE KATZ: Okay. Okay. So -- okay. Go ahead.

1 MS. BROWN-MARSHALL: Good afternoon, Your Honors.
2 May it please the Board. Christina Brown-Marshall on behalf of
3 Patent Owner Johns Hopkins University. I have with me co-counsel
4 Nicholas Stephens, Frank Scherkenbach, Kristi Sawert, Casey
5 Kraning, and Madelyn McCormick. And Ms. McCormick is going to
6 be presenting JHU's evidence of objective indicia.

7 From Johns Hopkins University, we also have representatives
8 Phil Roberts, Nicholas Tymoczko, Louisa Salomon, and Guido
9 Galvez. And unless Your Honors have any initial questions, I'd like
10 to jump right into the claim construction issue because I think it's
11 become evident that this is a very important issue for this IPR, and
12 that the sides are very far apart in their positions on this. So if I could
13 get slide number 4 please.

14 So the term in response to appears -- and is sort of a pivotal
15 issue in several different issues in this case. First of all, it's core to the
16 claimed invention in JHU's 393 patent. Merck's petition has
17 effectively ignored the in-response-to limitation in its analysis. And
18 Merck relies exclusively on the MSR as disclosing in-response-to for
19 all grounds. So it's anticipation ground, and in the one obviousness
20 ground in which it includes the independent claims. None of those,
21 neither the MSR, which it relies on in the anticipation ground; nor the
22 combination of the MSR and Pernot in ground 2 actually disclose
23 treating in response to determining that the patient is MSI-high.

24 And finally, you heard at the end of Petitioner's presentation,
25 their arguments relating to nexus. Again, they are relying on this

1 argument that in-response-to is indisputably known based on the
2 MSR. And that is the key to their nexus -- to their nexus argument.
3 And, again, these are all pivotal to the issues in this case. So if I could
4 get slide 5 please.

5 So just as a little bit of history about how we got here. So in the
6 petition and in Johns Hopkins' preliminary Patent Owner's response,
7 neither side proposed a construction for the term "in response to."
8 When the Board provided its institution decision, the Board construed
9 "in response to" as meaning after, and that was given as the
10 preliminary construction.

11 In JHU's Patent Owner's response, JHU has proposed the
12 construction "in reaction to." We believed that "in response to," the
13 plain and ordinary meaning was sufficient, but it seemed like there
14 was some confusion there. So we proposed the construction "in
15 reaction to, " and those are the two competing constructions that we
16 have in this case right now.

17 You heard Petitioner's counsel come up and say that we're
18 misrepresenting their position that they have no claim construction. I
19 didn't hear him provide any claim construction during his
20 presentation. He said that any construction will do. And, effectively,
21 any construction is no construction because they haven't identified a
22 construction.

23 But what they did do is in the District Court proceedings that
24 were occurring in parallel, they provided a claim construction to the
25 District Court. And they argued in the District Court that "in response

1 to" should be interpreted as as the reaction specifically to. That's very
2 similar to the construction that Johns Hopkins has offered in this case,
3 and it is contrary to the positions that Petitioner was providing when
4 they stood up. If I could, slide 6 please.

5 So in its Patent Owner's response, Johns Hopkins has provided
6 a full claim construction analysis supporting its construction of "in
7 response to" as in reaction to. We analyzed the claim language. We
8 analyzed the specification. We provided expert evidence on the plain
9 meaning to a person of ordinary skill. We talked about the examiner's
10 interpretation during prosecution of the patent. We showed dictionary
11 definitions. We've referenced Merck's previous construction. We
12 also cited Federal Circuit precedent that supports that "in response to"
13 should be construed as in reaction to.

14 For its part, Merck has not provided a claim construction
15 analysis. They didn't stand up here and point to evidence that "in
16 response to" should be construed as after. Instead they've done two
17 things. They've criticized JHU's analysis of the Board's construction.
18 And, remember, the Board's construction was made without the
19 benefit of having this claim construction evidence and claim
20 construction analysis before it.

21 They also argue that JHU's construction as an unclaimed
22 negative limitation. But if our construction in this IPR does that, so
23 did their construction in the District Court because they are so similar.
24 If I could get slide 7 please.

1 So with the two competing constructions of "in response to" in
2 mind, let's take a look at the claim language itself. So the 393 patent
3 has two independent claims, both of which recite an "in response to"
4 determining that the patient is MSI-high treating with an effective
5 amount of Pembrolizumab.

6 Those independent claims also have dependent claims, too.
7 And in the dependent claims, the inventors used the term after. So
8 they talk about, for instance in claim 7, "The patient's cancer has
9 progressed after the patient received the different cancer therapy."
10 Same thing with claim 20, which depends from independent claim 14.

11 So the inventors knew how to claim after. They knew when to
12 use after, but they chose for the independent claims to use the term "in
13 response to. " And that the tenant of claim construction, that different
14 words in the claim are given different meaning.

15 There's nothing in the specification, and Merck has not
16 identified any evidence that shows that the inventors intended for "in
17 response to" and "after" to mean the same thing. And construing "in
18 response to" as after would be a violation of that tenant that different
19 words have different meanings in the claims.

20 So next we look to the specification, and I think that there is an
21 important distinction that needs to be pointed out here. There is the
22 method that's disclosed in the MSR, which you heard Petitioner's
23 counsel speak about. There's also the claimed method, and those are
24 different methods.

1 So here in the summary of the invention where the specification
2 is talking about the claimed method, the invention itself, it discloses
3 testing for MSI-high and treating those MSI-high patients in response
4 to that determination.

5 The other thing that comes up in the summary of the invention
6 is it talks about this idea of microsatellite instability, identifying who's
7 a good candidate for treatment. Who are the patients who are going to
8 respond to treatment with Pembrolizumab? If I could get slide 9
9 please.

10 The other thing that the -- the other concept that the
11 specification introduces is this concept that patients who are MS
12 stable or MSI-negative, in other words, they're not MSI-high, those
13 are bad candidates for treatment because they're not going to respond
14 to treatment. And that appears in the specification at column 3, lines
15 62 through 67.

16 And this good/bad candidate gets to the concept the
17 specification is talking about. They're talking about using MSI as a
18 treatment selection marker for anti-PD-1 therapy. So it's this idea of
19 you test the patient, and their results trigger a determination. Yes,
20 they're MSI-high. They're a good candidate for treatment with anti-
21 PD-1 therapies such as Pembrolizumab. We treat them. No. they're
22 not MSI-high. They're not good candidates for treatment with anti-
23 PD-1 therapy. We're not going to treat them.

24 And I think counsel for Petitioner actually highlighted this for
25 us, and in a very nice way. So in the specification when it's talking

1 about the invention, it only talks about treating MSI-high patients.
2 And counsel pointed out that in this section of the specification, which
3 is found at column 13, lines 23 through 26 on the upper right hand of
4 slide 9, that's not talking about the invention.

5 That is talking about the clinical trial, the structure of which
6 was proposed by the MSR. Those are two different things. And the
7 MSR and the clinical trial that followed, both MSI-high and MSS
8 colorectal cancer patients were treated. Didn't matter what your MSI-
9 high status was because that was an evaluation.

10 The inventors had a hypothesis, and they wanted to test it. And
11 how you test it, you test it in both the MSI-high, and the MSS
12 patients, and you compare the results. And you see, is there a
13 difference? That is the evaluation stage. That was the MSR. That
14 was the clinical trial.

15 The inventors ran the clinical trial. They used those results to
16 support the claimed method. That's what we're talking about in that
17 summary of the invention. You test is a treatment selection marker.
18 If they are MSI-high, then you treat. If they're not MSI-high, then you
19 don't treat.

20 JUDGE KATZ: So where is the limitation in the claim of you
21 don't treat?

22 MS. BROWN-MARSHALL: So it is in the term "in response
23 to. "

24 JUDGE KATZ: That's a lot to put into three words.

1 MS. BROWN-MARSHALL: So I would say that the case law
2 supports that construction.

3 JUDGE KATZ: In terms of a clinical trial setting? Can you
4 cite me a case?

5 MS. BROWN-MARSHALL: So we cite --

6 JUDGE KATZ: Where --

7 MS. BROWN-MARSHALL: We don't --

8 JUDGE KATZ: Where a clinical trial would not be
9 anticipatory because the claim says don't do the other portion of the
10 clinical trial of the claim to treating the patient?

11 MS. BROWN-MARSHALL: So we don't have a case in the
12 clinical trial setting. We looked for one. I don't think it exists.

13 JUDGE KATZ: Okay.

14 MS. BROWN-MARSHALL: What we did is we looked at all
15 the cases we could find for "in response to, " and they come up in
16 different settings. The American Calcar v Honda case is in the
17 context of a vehicle generating notices. There are other cases that we
18 cited.

19 The Doggyphone v. Tomofun, Fujitsu v. Belkin, AnyLogic v.
20 TheBrain, none of those specifically dealt with clinical trials. But
21 they all support this idea that a person of ordinary skill in interpreting
22 the phrase in response to would understand that if it's in response to
23 one thing, it's not in response to something else. And I know counsel
24 pointed out that none of our cases touch on clinical trials. We would
25 have loved to have found a case that did, but --

1 JUDGE KATZ: Well, could that be because a claim to treating
2 is always about treating a patient. It's not about not treating a patient.
3 So how would claims -- I mean there are many claims about treating
4 patients, and all of those claims have -- the stuff has been through a
5 clinical trial. So there are many instances where there has been a
6 clinical trial, and then there are claims, and the claims sort of don't say
7 don't do everything else that was done in the clinical trial.

8 MS. BROWN-MARSHALL: So, Your Honor, I think it goes
9 back to this concept of a treatment selection marker. And the fact that
10 it is a two-step process that we're testing to determine if they are MSI-
11 high. And that's going to be the decision point whether they're going
12 to be treated if they are MSI-high or not treated if they're not MSI-
13 high.

14 JUDGE KATZ: Right. But it's a clinical trial that has to be
15 controlled. So how would you have a clinical trial -- how would you
16 be able to run a clinical trial without running into your claim unless
17 you had a sort of -- a claim that said don't treat other patients, which I
18 don't think anybody would ever write?

19 MS. BROWN-MARSHALL: So, Your Honor, it sounds like
20 you're describing sort of a late-stage clinical trial where you know that
21 your drug is going to work for its intended purpose, and you are
22 testing it against a control. So sort of the circumstances of the in re
23 Montgomery case. It's advanced. You're testing it in a lot of patients.
24 You're testing it against a control to see what the numbers are because
25 you're going to ready for regulatory application.

1 This was very different. This was a very early stage. And the
2 study -- the structure of the study shows that. If I could get slide
3 number 22 please.

4 So the MSR, which is the proposal for the clinical trial, said
5 that the study will be looking at whether MK3475, which is another
6 name for Pembrolizumab, or Pembro, will be looking at whether
7 Pembo is effective, shows anti-tumor activity, and safe in three
8 different patient populations. So they weren't using the MSS arm 2.

9 So if the first arm is MSI-positive colorectal cancer. The
10 second is the MSI-negative or MSS colorectal cancer. And the third
11 is MSI-high non-colorectal cancers. So the second arm is not a
12 control arm. That's not how they approached this. They were looking
13 and testing for safety and efficacy in both MSI-high and MSS
14 patients. If I could get --

15 JUDGE KATZ: It wasn't a control arm? It wasn't a
16 comparison arm? I mean you can -- what was it? I'm sort of
17 confused. I mean why would they have three separate arms if they
18 were just testing it in everybody? Why would they have divided them
19 into three separate arms?

20 MS. BROWN-MARSHALL: So, Your Honor, it's not a control
21 arm --

22 JUDGE KATZ: Okay.

23 MS. BROWN-MARSHALL: -- because they were both
24 experimental arms. They were both testing to see what their reaction
25 would be. And if I could, could I get slide 24?

1 So, Dr. Dung Le, who is one of the inventors on the 393 patent,
2 she was also the principle investigator for the clinical trial that was
3 proposed by the MSR. She explained in her declaration that they
4 approached this as a test to their hypothesis. That's what the clinical
5 trial was. They wanted to evaluate whether MSI could be used as that
6 treatment selection marker.

7 And she said that they approached this, it's not that arm 1 will
8 work in MSI-high patients, and arm 2 will not work in MSS patients.
9 That's not how they approached this. This was an experiment. They
10 were testing a hypothesis. And she said if we're correct, then we're
11 going to see a higher response in the MSI-high patients than the MSS
12 patients in arm 2.

13 JUDGE KATZ: Right.

14 MS. BROWN-MARSHALL: But she said, you know, we
15 could be wrong.

16 JUDGE KATZ: Do you have testimony from somebody who's
17 not an inventor that says that one skilled in the art would have looked
18 at those three arms and thought that they were not either -- I mean I'm
19 using the word control, but a control is a comparison to an
20 experimental branch. So do you have testimony from anybody, a non-
21 inventor to say that one skilled in the art would have looked at those
22 and thought that these are not comparisons?

23 MS. BROWN-MARSHALL: Yes, Your Honor. I believe we
24 have testimony from Dr. Lonberg, Dr. Nils Lonberg who is --

25 JUDGE KATZ: Okay.

1 MS. BROWN-MARSHALL: -- our expert. I don't have that
2 citation, but I can get it for you.

3 JUDGE KATZ: Okay.

4 MS. BROWN-MARSHALL: But that's how it was
5 approached. Right? This was an evaluation. They were looking at
6 what would be the response rate in MSI-high versus what would be
7 the response rate in MSS. And the results ended up being very
8 positive. There was significant response in the MSI-high patients, and
9 no response in the MSS patients.

10 JUDGE KATZ: So the drug had been used before, right, in
11 cancer patients of all types?

12 MS. BROWN-MARSHALL: So it had been used before in
13 some limited trials. It had been used in melanoma and non-small-cell
14 lung cancer. But the other point that's important is that Bristol Myers
15 Squibb, who had a similar drug, so it's another anti-PD-1 therapy, not
16 Pembrolizumab. It's called Nivolumab.

17 The inventors were initially running studies -- were initially
18 running studies looking at the use of Nivolumab in different types of
19 cancers. And they -- one of the types of cancers that they looked at
20 was colorectal cancer. And they tested it in 33 colorectal cancer
21 patients. Thirty-two of them had no response at all. One of them had
22 a complete response. And they couldn't explain why that one patient
23 would respond so well and the other 32 wouldn't.

24 JUDGE KATZ: Right. That's a published study, right? Is that
25 --

1 MS. BROWN-MARSHALL: Yeah. It comes out --

2 JUDGE KATZ: -- Exhibit 11 --

3 (Simultaneous speaking)

4 MS. BROWN-MARSHALL: -- published studies.

5 JUDGE KATZ: -- 57 or so. Is that --

6 MS. BROWN-MARSHALL: I'm sorry?

7 JUDGE KATZ: Is that the study that -- or it's not a study. Is
8 that the -- I think there's a paper that published that result.

9 MS. BROWN-MARSHALL: There's two separate papers.
10 There's the Topalian paper, and the Brommer paper. And I can get
11 those exhibit numbers for you.

12 JUDGE KATZ: Okay.

13 MS. BROWN-MARSHALL: And to answer your previous
14 question, the citation for Dr. Lonberg's declaration where he talks
15 about the three arms and describes them is Exhibit 2072 at paragraph
16 69.

17 JUDGE KATZ: Okay. I'm sorry. We were talking about the
18 published incidents of when the drugs seemed to work in an isolated
19 patient. So --

20 MS. BROWN-MARSHALL: So --

21 (Simultaneous speaking)

22 JUDGE KATZ: -- my question was, the drug had been used in
23 other patients, so this -- the MSR is not the first use of the drug in
24 patients? It wasn't just to see if this drug works at all, right, because

1 that had been done. I mean it was the drug that was being used in
2 patients already. Is that correct?

3 MS. BROWN-MARSHALL: It's correct that it was being used
4 in patients, but not colorectal cancer patients.

5 JUDGE KATZ: Okay. So you're saying that the point of the
6 MSR was to just use it in colorectal patients, period, to see if it
7 worked in colorectal patients at all? Is that the point of the MSR?

8 MS. BROWN-MARSHALL: So the MSR was proposing a
9 study. The inventors -- so Dr. Topalian and Dr. Pardoll who were
10 involved with the BMS study with Nivolumab spoke with some of the
11 other inventors who are geneticists, and they sort of had this eureka
12 meeting where they discussed -- they went to them and said we can't
13 explain this one patient's results. We don't know why this one person
14 responded and these other 32 didn't.

15 And the geneticists said, well, maybe take a look and see if
16 they're MSI-high. That might be an explanation. And so they went
17 back, and they tested that one patient for MSI-high, and it ended up he
18 was MSI-high.

19 JUDGE KATZ: Okay.

20 MS. BROWN-MARSHALL: And so they -- that's when they
21 designed this clinical trial. They reached out to BMS. BMS said, no,
22 we don't want to do that. It's too risky. Then they went to Merck, and
23 said Merck said, we'll give you drug, but we're not going to fund your
24 study. And that's when they proceeded with the clinical trial that did

1 this evaluation, you know, evaluating what's going to be the response
2 in MSI-high --

3 JUDGE KATZ: Compared to --

4 MS. BROWN-MARSHALL: -- comparing it to --

5 JUDGE KATZ: Right.

6 MS. BROWN-MARSHALL: -- MSS --

7 JUDGE KATZ: Okay.

8 MS. BROWN-MARSHALL: -- because we have an idea based
9 on one patient. Right?

10 JUDGE KATZ: Okay.

11 MS. BROWN-MARSHALL: And one patient is anecdotal
12 evidence. And they said we think -- this is our hypothesis. We want
13 to test this hypothesis. And that's what the clinical trial did. That's
14 what the MSR is proposing is for colorectal cancer patients, we're
15 going to test it in everybody. We think that MSI-high will explain --
16 will have a different result than MSS. We don't know. But we're
17 going to test them both.

18 We're going to administer the same dose of the drug to both of
19 them, and then we're going to compare the results and see if maybe
20 this MSI-high can be used as a treatment selection marker. And it did.
21 The results were fantastic, and were lauded by the ASCO and
22 published in the New England Journal of Medicine.

23 JUDGE KATZ: Right. So then getting back to the steps of the
24 claims, the step is to determine whether the patient is MSI-high, and
25 then treat the patient, which I hear is what was happening in the trial.

1 Patients were determined to be MSI-H, and then -- and in response to
2 that determination, they were treated.

3 MS. BROWN-MARSHALL: No. In the MSR, they were not
4 treated in response to the MSI -high determination because both MSI-
5 high and MSS patients were treated.

6 JUDGE KATZ: Right. The one patient who's --
7 (Simultaneous speaking)

8 MS. BROWN-MARSHALL: But the colorectal --

9 JUDGE KATZ: -- MSI-H was treated after being determined
10 to be MSI-H, right?

11 MS. BROWN-MARSHALL: They were treated after the
12 determination, but not in response to.

13 JUDGE KATZ: So they were treated after that -- you agree that
14 they were treated after the determination that they were MSI-H?

15 MS. BROWN-MARSHALL: So the MSR is silent as to
16 testing. So it actually doesn't say whether or not, but even if you
17 assume that they were all tested and the determination was made
18 before, they were still not treated in response to because, effectively,
19 that response had no bearing on the decision whether or not they
20 would be treated because all of the colorectal cancer patients were
21 going to be treated no matter how the -- you could have not run the
22 test.

23 You could run it, and it could come back MSI-high. You could
24 run it, and it could come back MSS. It doesn't matter because all of

1 the colorectal cancer patients in the study proposed by the MSR are
2 treated the same way. And Merck does not dispute that.

3 JUDGE KATZ: Okay.

4 MS. BROWN-MARSHALL: So if we could -- going back to
5 claim construction, I would like to address one point that came up
6 during Petitioner's arguments. As we mentioned that, you know, in
7 the parallel District Court proceedings, Merck has proposed a
8 construction of as the reaction specifically to. And we would argue --
9 oh. And one other thing to point out.

10 So for the MSI-high and the MSS patients that were treated in
11 the study proposed by the MSR, for the colorectal cancer patients,
12 those patients were treated in response to enrollment. Everyone who
13 was enrolled was treated the same way. Not in response to any
14 determination of MSI-high or MSS, just as a point of clarification. So
15 back to Merck's proposed construction.

16 JUDGE NEWMAN: I have a question regarding that. But if
17 we were looking -- if the study was done to look for MSI as a
18 predictive marker, doesn't it then make sense that the patients would
19 have been selected based on their MSI-high marker status or MSI --
20 whether they had it or not, they were looking for that when designing
21 the study, correct?

22 MS. BROWN-MARSHALL: No, Your Honor, I would
23 disagree because for the colorectal cancer patients, they needed both.
24 Right? If we're doing an evaluation, we're going to compare the

1 response in those two groups, then they had -- then they needed both
2 of them.

3 And therefore, for the colorectal cancer patients, they're treated
4 in response to enrollment. If you're a colorectal cancer patient and
5 you're enrolled in the study, you're treated the same way. And your
6 MSI-high determination is not relevant for the sake of the treatment
7 decision.

8 JUDGE NEWMAN: But wouldn't the study not be effective in
9 determining that it was a predictive marker whether or not some MSI-
10 high patients enrolled in the study?

11 MS. BROWN-MARSHALL: Yes, Your Honor. But the same
12 thing could be said for the MSS patients. The MSI-high patients need
13 to be present, but MSS patients also need to be present, too, because
14 you can't do an evaluation unless you're treating both groups, and
15 you're treating them both the same way and you're comparing the
16 results.

17 JUDGE NEWMAN: Yes. But you would have had to have
18 had some of all in order to generate enough statistically significant
19 responses to be able to determine that it was predictive marker.

20 MS. BROWN-MARSHALL: Yes, Your Honor. There would
21 have had to have been some MSI-high patients colorectal cancer
22 patients in the study just as there would have to be some MSS
23 colorectal cancer patients. And they were both treated the same way.

24 JUDGE NEWMAN: So understanding that it doesn't make
25 sense that there was no testing done, otherwise you would not have

1 created enough statistically significant responses in order to compare
2 those patient populations. Can you comment on that?

3 MS. BROWN-MARSHALL: Yes, Your Honor. And I think
4 this goes to the distinction between the MSR and the clinical trial
5 itself. So in the MSR, it proposes a study that has two arms, and it's
6 silent as to testing. I think it's reasonable to conclude that testing
7 would have to be done at some point, but it doesn't say that you have
8 to be tested to be enrolled.

9 But they would still enroll both MSI-high and MSS patients,
10 you know, eventually, and I think Doctor -- JHU's expert Dr.
11 Goldberg said that as the clinical trial itself progressed, then you did
12 have a position where, you know, one arm filled up, and the other arm
13 didn't. That is the clinical trial. That's not the MSR. The MSR in the
14 proposal just says that there's two arms, and it doesn't say that you
15 have to be tested before you're enrolled, or as a colorectal cancer
16 patient, you can be enrolled and then tested and assigned to an arm.

17 JUDGE NEWMAN: All right. I understand your argument.

18 MS. BROWN-MARSHALL: Okay. Thank you. And if I
19 could get slide number 13, please. So this is coming from Merck's
20 claim construction briefing in the District Court. And in their claim
21 construction briefing, they say that their construction, which is "as the
22 reaction specifically to."

23 So addressing that alleged negative limitation that they are
24 saying that John's Hopkins is adding in their construction, they say
25 this construction is consistent with the intrinsic record which focuses

1 on MSI-high as a determining marker for whether a cancer patient
2 should be treated with Pembrolizumab.

3 That is the construction that JHU is proposing. We're talking
4 about the treatment selection marker for whether a cancer patient
5 should be treated. So that's looking at this yes or no. If they are MSI-
6 high, then we treat. If they're not MSI-high, then we don't treat.
7 Merck adopted this in the District Court.

8 I'd also like to point out counsel made a comment about our
9 alleged misleading citation when we cited to the specification when
10 we were talking about the claim selection marker. If you look at the --
11 it's the fourth line down, they cite to that same spot in the
12 specification, column 13, line 24 to 26.

13 It's not misleading. That is the description of the clinical trial
14 where MSI-high and MSS colorectal cancers are both treated. That's
15 not the claim method where MSI-high is treated, and MSS colorectal
16 cancer patients are not treated. If I could get slide number 16.

17 So we talked about Johns Hopkins case support for its
18 construction. I think it's worth pointing out a few aspects about the
19 case law that Merck relies on in support of its claim construction
20 positions, whatever those are.

21 Merck relies on the Omega Engineering case that it cites here
22 on slide 16, which is taken out of their reply briefing. Omega
23 Engineering is not a case about clinical trials. It's a case about lasers.
24 It doesn't address the claim limitation "in response to. " It actually
25 deals with a (inaudible) function claim that has to do with a laser. It's

1 readily distinguishable from the case -- from this case where we're
2 using "in response to" to talk about treatment selection between MSI-
3 high and MSS cancers.

4 JUDGE KATZ: But would you agree sort of in general that we
5 shouldn't read an unclaimed negative limitation into a claim, now
6 whether it is here or not? But that seems to be a pretty basic
7 fundamental that we don't read limitations into claims that aren't there,
8 negative or positive?

9 MS. BROWN-MARSHALL: So, Your Honor, I would say that
10 we shouldn't read an unclaimed limitation, but in this instance, it is a
11 claimed limitation.

12 JUDGE KATZ: If it's within the three words of "in response
13 to? "

14 MS. BROWN-MARSHALL: Yes, Your Honor.

15 JUDGE KATZ: Okay.

16 MS. BROWN-MARSHALL: It's in the term itself "in response
17 to. "

18 JUDGE KATZ: Okay. So you're actually -- your problem is
19 whether those -- your problem with the citation is not to sort of what
20 the citation is saying. It's to the -- it goes back, again, to the claim
21 construction. Not sort of the idea of reading unclaimed negative
22 limitations into claims?

23 MS. BROWN-MARSHALL: Yes, Your Honor.

24 JUDGE KATZ: Okay.

1 MS. BROWN-MARSHALL: So we don't have to claim not
2 treating the MSS colorectal cancer patients because that's in --

3 JUDGE KATZ: Right.

4 MS. BROWN-MARSHALL: --the claim itself.

5 JUDGE KATZ: Right.

6 MS. BROWN-MARSHALL: And a person of ordinary skill
7 would understand that.

8 JUDGE KATZ: Okay.

9 MS. BROWN-MARSHALL: And, finally, our last point on
10 claim construction, if I could get slide 17 please. So in the institution
11 decision, the Board touched on, you know, whether or not there is this
12 causal relationship between testing for MSI-high, and treating the
13 MSI-high cancers after determining. And it's JHU's position that that
14 construction doesn't appropriately capture this causal relationship.

15 JUDGE KATZ: Can there be a causal -- even though we said
16 after, can there still be a causal relationship even though we described
17 it in a timing way?

18 MS. BROWN-MARSHALL: So I think the causal relationship
19 has two components. There is a temporal -- there is a temporal
20 component to it. If you're making a decision in response to a piece of
21 information, you have to have that piece of information first.

22 So I think the problem is is that the Board's construction doesn't
23 get you all the way there. It captures that temporal relationship, but it
24 doesn't capture that cause and effect relationship that is built into "in
25 response to" where you say, yes, if you determine that they are MSI-

1 high, then treat. And if you determine that they're not MSI-high, then
2 you don't treat.

3 That's what's missing from the Board's preliminary
4 construction. And if you don't have that second piece, you render that
5 in-response-to limitation in the claim meaningless because it doesn't
6 mean anything because, effectively, you test for MSI-high, and you
7 just ignore it and you treat everyone.

8 JUDGE KATZ: Well, you test for MSI-high, and then in
9 response to testing for MSI-high, you treat.

10 MS. BROWN-MARSHALL: But it's not in response to testing.
11 It's in response to determining that the patient is MSI-high. And that
12 determination --

13 JUDGE KATZ: Right. Okay. So you determine that the
14 patient is MSI-high, and then you treat.

15 MS. BROWN-MARSHALL: But it's not in response to.
16 There's not that cause and effect relationship.

17 JUDGE KATZ: Okay. I understand your argument.

18 MS. BROWN-MARSHALL: Okay.

19 JUDGE SNEDDEN: The MSR teaches treating MSI-H
20 patients, right?

21 MS. BROWN-MARSHALL: So it teaches treating MSI-high
22 colorectal cancer patients in arm 1. And then in arm 2, it teaches
23 treating MSS colorectal cancer patients.

1 JUDGE SNEDDEN: Okay. But the argument is that they're
2 not treated in response to determining whether or not they have it
3 treated, but was it in response to figuring out if they have MSI-H?

4 MS. BROWN-MARSHALL: According to the MSR, all
5 colorectal cancer patients are treated in response to enrollment. Once
6 you're in, you're getting treated. Doesn't matter if you're MSI-high or
7 if you're MSS.

8 JUDGE SNEDDEN: Okay. How do we avoid the inherency
9 arguments here, if the patients had MSI-H, and yet they were treated?

10 MS. BROWN-MARSHALL: So, Your Honor, are you
11 referring to the in re Montgomery case? We're talking about the
12 outcomes of the trial being inherent in the disclosure of the trial?

13 JUDGE SNEDDEN: Sure. Yeah.

14 MS. BROWN-MARSHALL: Okay. So I think -- let's --

15 JUDGE SNEDDEN: Well -- yeah. Please go ahead.

16 MS. BROWN-MARSHALL: Okay.

17 JUDGE SNEDDEN: Just -- yeah.

18 MS. BROWN-MARSHALL: So if I could get slide 33 please.
19 So Merck is relying on -- actually, slide 32 please. So Merck is
20 relying on the in re Montgomery case as saying that the disclosure of
21 a planned clinical study proposing a method of treatment anticipates
22 even if the study is not performed. And it's this concept of the results
23 of the study are inherent.

24 If you proposed the study, even if you haven't conducted it, the
25 results are going to be what they're going to be because those are in --

1 the results are inherent in the disclosure of the study itself. And that
2 flows from this concept that the inherent result must inevitably result
3 from the disclosed steps, and that is -- where, factually, we can
4 distinguish the situation here with the MSR, which proposed Johns
5 Hopkins' study and the proposed -- the study proposal in re
6 Montgomery. If I could get slide 33.

7 So there are multiple reasons why the current situation is
8 distinguishable from in re Montgomery. So, first, at the time that it
9 was published, the HOPE Study, which is the study disclosure in re
10 Montgomery, disclosed that the claimed drug had been administered
11 to a large number of the claimed patients. Here the study hadn't
12 started yet. It was just a proposal. Hadn't enrolled any patients.
13 Hadn't treated any patients.

14 Second, the HOPE Study's disclosure was in all relevant aspects
15 identical to the patent. So the study -- the clinical study proposal and
16 the patent itself were in all relevant aspects identical. Here, they're
17 very different. So if we look at slide 33, the 393 patent disclosure
18 does not include the MSR. The 393 patent disclosure, the
19 specification is based on an New England Journal of Medicine article
20 that was published with results of the clinical trial itself, and that
21 forms the basis of the specification.

22 Further, the method disclosed in the MSR, and the method that
23 is claimed are different. Remember, in the MSR, you're treating both
24 MSI-high and MSS colorectal cancer patients. In the claim method,
25 you're only treating MSI-high patients, and not treating MSS patients.

1 Third distinction, the Montgomery patent didn't disclose any
2 data. Didn't disclose any clinical trials. Didn't talk about the need for
3 any clinical trial to support the claims of the Montgomery patent.
4 This is very different. The JHU inventors were testing their
5 hypothesis. They needed to run the clinical trial to know that it would
6 work in order to have support for their claimed method of treatment
7 where you treat MSI-high colorectal cancer patients, and you don't
8 treat MSS colorectal cancer patients.

9 The Federal Circuit also explained that the HOPE Study in the
10 in re Montgomery case was far from an abstract theory, an advanced
11 stage of testing designed to secure regulatory approval, and supported
12 by a substantial evidence. Here, the MSR was the epitome of an
13 invitation to investigate.

14 And Petitioner's counsel pointed out that that invitation to
15 investigate language is in the dissent. The majority opinion also
16 acknowledges, to be sure, as the dissent points out, an invitation to
17 investigate is not an inherent disclosure. So that's appropriate to cite
18 because the majority adopted that position, too.

19 The fifth distinction, in Montgomery, the Patent Owner
20 conceded that the authors of the HOPE Study could have sought the
21 same claims based on their study proposal as he was seeking in his
22 patent here. Johns Hopkins couldn't have received those claims
23 because the results of the trial were necessary to provide 112 support
24 for the claimed methods.

1 And, finally, Montgomery didn't raise an experimental use
2 argument. In that case, it was a question solely of inherency. Here,
3 JHU has demonstrated that the MSR qualifies for an experimental use
4 exception. And Merck has not rebutted any of the evidence that Johns
5 Hopkins has provided to support that contention. So, Your Honor,
6 does that answer your question?

7 JUDGE SNEDDEN: Yes.

8 MS. BROWN-MARSHALL: Okay. Great.

9 JUDGE KATZ: So if there was a clinic that didn't do MSI
10 testing and just treated all colorectal cancer patients with the drug --
11 with Pembrolizumab, would they fall under your claims? Would they
12 be practicing within the scope of your claims?

13 MS. BROWN-MARSHALL: No, Your Honor. It's our
14 position that if you are treating colorectal cancer patients with
15 Pembrolizumab without testing for MSI-high or ignoring what the
16 MSI-high results are and treating both MSI-high and MSS, you would
17 not be practicing the claims. And that's consistent with the disclosure
18 of the MSR, not practicing the claims.

19 JUDGE KATZ: Okay.

20 MS. BROWN-MARSHALL: I would like to touch on very
21 quickly --

22 JUDGE KATZ: So, actually, let me follow that up with
23 something. So you are saying that the scope of your claims is sort of
24 at a clinic level, not a particular patient level?

25 MS. BROWN-MARSHALL: Well --

1 JUDGE KATZ: It's like a -- it's a practice of medicine. It's not
2 actually treating a patient.

3 MS. BROWN-MARSHALL: No, Your Honor. I would say
4 that it is directed to treating a patient because even though it's
5 practiced at a clinic level, you're making the treatment decision for
6 each individual patient. And you're making the treatment decision
7 based on the determination of that individual patient's MSI-high
8 status.

9 JUDGE KATZ: So if there's a doctor who treated only one
10 patient for colorectal cancer, and did find that they were MSI-high, or
11 one doctor who didn't find that they were MSI-high, that -- how would
12 you evaluate whether they were within the scope of your claim
13 because you don't know whether they treated other patients in
14 response to or not?

15 MS. BROWN-MARSHALL: So, Your Honor, I would say in
16 the real world setting where you have a doctor who's actually treating
17 MSI-high patients, they are treating according to the label that
18 accompanies Keytruda, which is Merck's Pembrolizumab product,
19 which the label tells you to test for MSI-high for colorectal cancer
20 patients, and to treat MSI-high colorectal cancer patients.

21 So I would say that that individual doctor, even if they're only
22 treating one patient, he's treating under that FDA-approved indication
23 that's on the label which encapsulates and that practices the claims of
24 the JHU patent.

25 JUDGE KATZ: Okay.

1 MS. BROWN-MARSHALL: Yeah. Another good point is that
2 if that doctor were treating non-MSI-high patients, colorectal cancer
3 patients with Pembrolizumab, it wouldn't work. So there's a potential,
4 you know, malpractice issue in there that you're treating an individual
5 patient with a drug that is shown not to be effective in --

6 (Simultaneous speaking)

7 JUDGE KATZ: Right. But that's not our -- that's not my
8 question.

9 MS. BROWN-MARSHALL: Yeah.

10 JUDGE KATZ: But, okay. All right. Thank you.

11 MS. BROWN-MARSHALL: So, Your Honors, I'd like to turn
12 very quickly to experimental use. So if I could get slide number 41.
13 And we heard during Petitioner's presentation that Johns Hopkins
14 hasn't cited any case law that says that a printed publication cannot
15 qualify for experimental use.

16 The reality is that there aren't cases that go in either direction.
17 There are no cases that say a publication can qualify for experimental
18 use. But there's also no publications that say that it can't qualify for
19 experimental use. And they point to the Celltrion and the Salix cases
20 as showing instances where a submission to ClinicalTrials.gov was a
21 prior art reference used in invalidating a patent.

22 We're not asking for a categorical exclusion of submissions to
23 ClinicalTrials.gov as prior art publications. It's JHU's position that if
24 a clinical trial itself can qualify for the experimental use exception,
25 then the proposal that proceeds that clinical trial should also be able to

1 qualify. Not categorically, but that you should apply the same test
2 that you would apply to the clinical trial itself. You should go through
3 the factors and determine whether or not experimental use applies.
4 And that's that we've done.

5 You can see on slide 41 you see a list of all of the factors that
6 we've provided evidence that the MSR meets. We've provided
7 testimony from Dr. Le, who is one of the inventors, and also the
8 principal investigator on the trial. We provided evidence from Ms.
9 Jennifer Newberger who is a regulatory expert who talked about the
10 requirements for the disclosures that are necessary for
11 ClinicalTrials.gov in order to -- in order to be able to carry out that
12 clinical trial. So what we ask is just that the MSR, the submission to
13 ClinicalTrials.gov be evaluated under the same rubric for potential
14 experimental use as you would a clinical trial itself.

15 And one thing to point out, too. The 393 patent is a post-AIA
16 patent. So under the AIA, there's only one category of prior art. So it
17 wouldn't make sense from a statutory perspective or from a policy
18 perspective for the experimental use exception to apply to some of the
19 one category of prior art and not others.

20 So we've touched on the MSR, and Merck's argument that MSR
21 anticipates that the claims of the 393 patent, and we talked about it in
22 the context of "in response to." And I just wanted to quickly touch on
23 some of the other limitations that Merck also say is disclosed by the
24 MSR. So if I could get slide 26 please.

1 JUDGE SNEDDEN: Are these limitations for dependent
2 claims? Or --

3 MS. BROWN-MARSHALL: Yes. These are the dependent
4 claims.

5 JUDGE SNEDDEN: Before we move on, let me just ask a
6 question. I think I understand your arguments. So I'm going to ask a
7 question just to make it clear. When we look -- when we were
8 looking at the MSR, arm 1 teaches basically treating patients with the
9 MSI-positive colorectal cancer, and that's the MSI-H.

10 And your argument is that they were treated. They were treated
11 because they were enrolled in a study. And that -- but they weren't
12 treated because they were determined to have it. So in that regard, the
13 MSR does not teach the in-response-to limitation?

14 MS. BROWN-MARSHALL: Correct.

15 JUDGE SNEDDEN: That's basically the argument. Okay.

16 MS. BROWN-MARSHALL: Correct.

17 JUDGE SNEDDEN: Thank you. I understand.

18 MS. BROWN-MARSHALL: Okay. So on slide 26, we
19 highlight some of these other limitations in the dependent claims that
20 are not present in the MSR, not disclosed by the MSR. We talked
21 about the outcomes measures and why in re Montgomery is not
22 applicable in this case -- is distinguishable in this case.

23 For the other -- for the other limitations, so received a different
24 or prior cancer therapy, progressed on a different prior cancer therapy,

1 and metastatic colorectal cancer, the MSR doesn't disclose any of
2 those. It doesn't talk about those explicitly.

3 You'll see that in Merck's presentation. They sort of had to
4 piece together different pieces as to why a person of ordinary skill
5 would understand that even though it's not disclosed in the MSR, that
6 it's present there. So essentially, they're making an inherency
7 argument.

8 They're saying that these limitations are inherent in the
9 disclosure of the MSR. But they don't meet the high bar that's
10 necessary to show that those are inherently present. So they provide
11 no evidence, opinion, or argument that these limitations are
12 necessarily present in the MSR.

13 So in Dr. Neugut's declaration, he talked about how on slide 28,
14 the person of ordinary skill would have understood that treating
15 patients who received a prior therapy and progressed was found in the
16 MSI-high study record, but it doesn't say that it's necessarily present.

17 And the reason why he doesn't say that it's necessarily present,
18 as we see on slide 29, is that when we asked Dr. Oberstein, who is
19 Merck's second oncology expert that they presented in these
20 proceedings, you know, would a patient who is otherwise qualified
21 under the inclusion and exclusion criteria in the MSR not be excluded
22 from this clinical trial if they had not received a prior therapy because
23 of an allergy, which is just one example, to the available
24 chemotherapy, which was the prior therapy available at the time.

1 So I don't think a POSA can determine if that person was
2 excluded or not based on what's available in the MSR. And Dr.
3 Oberstein goes on to say it does not speak to that point. So the MSR
4 is silent as to whether or not a person who had not received a prior
5 therapy could be included. And you can't conclude that that limitation
6 is necessarily present based on that silence. And if I could get slide
7 30.

8 Similar argument for metastatic cancer, Dr. Oberstein, Merck's
9 expert, has said that the MSI-high study record requires metastatic
10 cancer or cancer that is so locally advanced it's (inaudible) for
11 purposes of a cure. So it's not -- metastatic colorectal cancer is not
12 necessarily present if it can be fulfilled by two different options. So
13 that is not necessarily present in the dependent claims of the 393
14 patent.

15 And going back to our arguments about the in re Montgomery
16 case and the inherency of the outcomes-related limitations, if I could
17 get slide number 37. So JHU has presented evidence on why the
18 MSR is this invitation to investigate that the Federal Circuit found
19 was not an inherent disclosure.

20 So the Johns Hopkins inventors had a hypothesis based on that
21 one MSI-high patient that was treated with a different drug, and
22 responded to that treatment, one MSI-high colorectal cancer patient.
23 He was treated with a different drug and responded. The only study
24 on PD-1 inhibitors, so that's the Nivolumab, the BMS study, had a 97

1 percent failure rate. So other than that one patient, 97 percent of the
2 people failed on that treatment.

3 Another important point is there is no animal data to support
4 this hypothesis because there are no good animal models for MSI-high
5 cancers. So this was not something where you could go test it in a
6 mouse first, and maybe you have an idea based on that clinical data,
7 that animal data, maybe this will work, this will not work.

8 As Dr. Le, one of the JHU inventors and the PI of the clinical
9 trial, said this nice thing when she said the clinic is the experiment.
10 You have to test this in people because we don't have a good animal
11 model. And so Merck's position that it would be outlandish to put this
12 in people when you didn't know is just not true. That was the only
13 way that they could test that is to propose this clinical trial where they
14 tested it in both MSI-high colorectal cancer patients and MSS
15 colorectal cancer patients.

16 No patients were enrolled or treated in the clinical study
17 proposed by the MSR. And both BMS and Merck were skeptical of
18 the study. Merck has not rebutted any of that evidence. All of that
19 supports our position that the MSR was an invitation to investigate
20 and not an inherent disclosure under Montgomery. And if I could get
21 slide 39.

22 Just a quick point before we move on from anticipation. You
23 know, Johns Hopkins has made three parallel arguments that are all
24 internally consistent. We've said that the MSR is an invitation to
25 investigate because it was very early. It was an abstract idea that was

1 testing a hypothesis. That's consistent with our experimental use
2 argument.

3 This was very early. The clinical trial needed to be conducted
4 because the primary purpose was experimentation to find out if MSI
5 could be used as a treatment selection marker in these groups of
6 colorectal cancer patients. It's also consistent with the arguments of
7 timing. I know that Merck had highlighted that potentially Johns
8 Hopkins could have just applied for their patent earlier.

9 So Johns Hopkins actually has an earlier provisional patent
10 that -- a provisional application. We're not claiming priority to that
11 because that earlier application didn't have any data in it. No data, no
12 112 support. We are claiming priority to the earliest application that
13 had the data in it because that's what was needed in order to provide
14 written description support for the claims.

15 And if Your Honors don't have any other questions, I'd like to
16 move on to obviousness very quickly. Okay.

17 JUDGE KATZ: Okay. Thank you.

18 MS. BROWN-MARSHALL: So if I could get slide 44. So
19 Merck's obviousness arguments fail for three reasons. First, the prior
20 art that they cite does not disclose "in response to." They only have
21 one obviousness ground that addresses the independent claims that
22 contain the in-response-to limitation, and that's ground 2, which is the
23 combination of the MSR and Pernot. As we've talked about in the
24 anticipation setting, the MSR doesn't disclose "in response to." And if
25 we could go to slide 47

1 Dr. Neugut, when we asked him, "You're not relying on Pernot
2 for disclosing the in-response-to claim limitation, right?" "Correct."
3 If they're not relying on Pernot, then the MSR has to provide that in-
4 response-to limitation for their obviousness arguments, and it doesn't.
5 So all of their obviousness grounds fail.

6 Merck has also failed to establish a reasonable expectation of
7 success. If I could go to slide number 42. I'm sorry, 52. In order to
8 establish a reasonable expectation of success in the claimed
9 treatment -- because that's what we're looking is reasonable
10 expectation of success in the claimed treatment.

11 And I notice that counsel used the language talking about a
12 reasonable expectation of success in carrying out the MSR. That's not
13 our focus for reasonable expectation of success. The reasonable
14 expectation of success should be focused on expectation of success in
15 using the claimed method. Slide 53.

16 So we talked about this a little bit in the context of the
17 invitation to investigate. Cancer therapy is very unpredictable. For a
18 reasonable -- and there's no animal models of MSI-high cancers.
19 There are no PD-1 inhibitors that have been approved for any
20 indication prior to the submission of the MSR.

21 And the way that cancer patients were treated, at the time MSI-
22 high and MSI-stable patients were treated the same way. This was not
23 something where in other cancers, you know, there was a distinction
24 between those two, and that that was sort of something that doctors
25 were thinking about. They were treated the same way.

1 And Merck has identified clinical trials where they say, well,
2 there were MSI-high -- there must have been MSI-high patients in
3 those clinical trials because those are types of cancer where -- are
4 known to have some MSI-high patients. But they weren't identified.
5 They weren't looked at. They were only identified retrospectively. So
6 there's not this data on how do MSI-high cancer patients respond to
7 certain drugs. That was not out there. That was not being tested in
8 the clinical --

9 (Simultaneous speaking)

10 JUDGE KATZ: So your third point, though, isn't the --
11 shouldn't the date be the date of your provisional application? I think
12 that was Petitioner's argument. We're looking at this as of the date of
13 your provisional application in 2015. Not as of the date of the MSR
14 posting. Is that correct?

15 MS. BROWN-MARSHALL: So you're correct, Your Honor,
16 that you look at reasonable expectation of success as of the critical
17 date, which is July 10th, 2015. We're sort of setting the stage of
18 where things were when the MSR was filed. We can address, you
19 know, Petitioner cited several different references for reasonable
20 expectation of success that fall in the 2014 period. But it's our
21 position that none of those references actually provide a reasonable
22 expectation of success.

23 JUDGE KATZ: But I think -- I mean for our purposes, we
24 have to focus on the 2015 date. Not sort of setting the stage in 2013.

1 We'll be looking for a reasonable expectation of success as of your
2 critical date.

3 MS. BROWN-MARSHALL: Correct.

4 JUDGE KATZ: Okay.

5 MS. BROWN-MARSHALL: Correct. And you need to look at
6 the references that Merck has cited that they allege provide that
7 reasonable expectation of success. And I think Pernot is a good
8 example. If we could turn to slide 58.

9 So the statement in Pernot that Petitioner is relying on, and as
10 their evidence of reasonable expectation of success fails to provide
11 that for two different reasons. First of all, the statement, which is just
12 that colorectal cancer associated with MSI could lead to more intense
13 immune response, but also to specific immunoregulatory phenomena
14 making them good candidates for immunotherapy.

15 And, Judge Katz, as you honed in on, immunotherapy is a very
16 broad term. And there is nothing but hindsight that connects that
17 recommendation of these might be good candidates for
18 immunotherapy to saying that in MSI-high colorectal cancer, that
19 there's any reasonable expectation of success that those cancers are
20 going to respond to treatment with Pembrolizumab or even an anti-
21 PD-1 inhibitor.

22 The other reason why Pernot doesn't disclose reasonable
23 expectation of success is it ignores other sections in Pernot that teach
24 away from using immunotherapies for colorectal cancer patients.
25 They like to focus on that cherry-picked sentence that says something

1 that they like. But they ignore the context of Pernot, which says that
2 there's all these reasons why colorectal cancer wouldn't be good for
3 treating immunotherapy.

4 And we can see on slide 66, it talks about -- Pernot talks about
5 potential major obstacles to the establishment of an effective immune
6 response, but also to the use of immunotherapy in colorectal cancer
7 patients. And the only way that you can draw a straight line between
8 that one sentence in Pernot and the success of JHU's claimed method
9 is with hindsight. If I could get slide 63.

10 And just to point out, so in the Pernot article, they actually
11 provide a table. This is table 1 from Exhibit 1006, that lists ongoing
12 clinical trials according to the National Cancer Institute registries
13 using immunotherapy according to the strategy.

14 So they have identified 27 different ongoing clinical trials of
15 immunotherapy involving six types of immunotherapy strategies.
16 And these are the ongoing trials of interest that Pernot is focusing on.
17 None of these trials included an anti-PD-1 therapy, let alone
18 Pembrolizumab.

19 And Merck, in their reasonable expectation of success, likes to
20 point out that they give the impression that as of 2014, when Pernot
21 was published, that the conclusions of the -- of JHU's clinical trial
22 were a foregone conclusion. Everyone knew it was going to work.
23 Well, Pernot selected these 27 clinical trials, and highlighted them in
24 his article. He didn't include the JHU clinical trial.

1 And we are running short on time, but if I could get slide 67. I
2 would just point out that Merck has identified several different
3 references from this 2014 time period. The Gatalica reference, the
4 Brown reference, the Champiat reference, the Ogino reference.

5 These have the same problems as Pernot. They're pointing out
6 these broad categories of cancer, broad categories of
7 immunotherapies. And they're saying a person of ordinary skill would
8 draw the line and say, yes. When they talk about highly mutated
9 cancers, they're talking about MSI-high cancer. And, yes, when they
10 talk about good candidates for immunotherapy, they must have been
11 talking about anti-PD-1 therapy. But the only way you can make that
12 connection is with the benefit of hindsight. So, actually, if we could
13 get slide 67, Merck slide 67. Or, actually, Casey, never mind.

14 So in the Gatalica reference, they talk about, you know, it
15 includes this speculative expression of hope that PD-1 and PDL-1
16 expression would be connected to some sort of response to targeted
17 immunotherapies. Again, if I could get our slide 60. Our slide 60.
18 Thank you.

19 Again, we're talking about this broad category of
20 immunotherapies. Dr. Nils Lonberg, who is the JHU expert,
21 identified seven different categories of immunotherapies. Dr.
22 Oberstein, who's Merck's expert, identified that he is actually
23 participating in a clinical trial in which they're testing exercise as a
24 potential immunotherapy. So it's a very, very broad category.

1 One of those categories underneath the umbrella term of
2 immunotherapy is immune checkpoint inhibitors, which is what the
3 anti-PD-1 therapies fall under. But even under that category, you
4 have different types of immune checkpoint inhibitors. You have
5 CTL-4. You have PD-1, PDL-1. And you have LAG-3, which are all
6 three that are in existence now. And even within the PD-1, you can
7 have this related antibody therapies that attack PD-1, or its
8 compliment, PDL-1.

9 So to go from this very broad umbrella term of cancer
10 immunotherapies all the way down to anti-PD-1 therapies, and
11 Pembrolizumab specifically, the only way you can do that, the only
12 way you can trace that pathway is with hindsight. Otherwise, there's
13 no reasonable expectation of success based on Pernot or any of those
14 other references cited by Merck that make these broad speculative
15 statements.

16 And that is based on -- that is based on the OSI Pharma case, if
17 I could get slide 54. And OSI Pharma highlighted that hope that a
18 potentially promising drug will treat a particular cancer is not enough
19 to create a reasonable expectation of success. And that's all that these
20 references highlighted is a hope that maybe these will be good
21 candidates for immunotherapy. If I could get slide 55.

22 And, again, remember, we're in the context of the baseline at
23 which the Johns Hopkins inventors approached their hypothesis and
24 their clinical trial testing that hypothesis, the baseline was failure. We
25 had one clinical trial anti-PD-1 therapies in colorectal cancer patients,

1 and it had a 97 percent failure rate. It worked in one patient. And
2 OSI Pharma says given a 99.5 percent failure rate, the only reasonable
3 expectation at the time of the invention was failure, not success.

4 That's the situation we were in here. That's the situation that
5 the JHU inventors were in. The only data that they had pointed to
6 failure. And so when you're looking at these sort of cherry-picked
7 sentences from various references that Merck relies on to support its
8 arguments about reasonable expectation of success, remember that
9 that has to be considered against that baseline. That baseline is this
10 doesn't work in this type of cancer.

11 And when you consider that, when you consider all of the
12 evidence, even at the critical date on July 10th, 2015, the reasonable
13 expectation of time is failure. It's not success according to OSI
14 Pharma. If I could get slide 70 please.

15 So, again, the baseline at the time, the expectation was that this
16 was -- the anti-PD-1 therapies were not going to work in colorectal
17 cancer patients. If I could get the next slide please. And even looking
18 at that one patient who did respond, just as reported in the Lipson
19 article, which is Exhibit 1057.

20 So Dr. Chapelle and Dr. Pardoll, who are both inventors on the
21 JHU patent, they were working on the study using BMS's Nivolumab
22 drug. And they saw this one patient who responded when 32 others
23 didn't respond. And they included that in this publication, and they
24 talked about we have this one patient who responded. And at the

1 time, they noted that the patient was MSI-high, but they didn't make
2 any conclusions based on that.

3 And if you actually look at what they were thinking at the time
4 when they published this, the correlation between tumor cell
5 membrane PDL expression, which remember, PDL is the compliment
6 to PD-1, and the likelihood of response to anti-PD-1 therapy, potential
7 relationships between PDL-1 expression on non-tumor cells and
8 clinical outcomes require further study.

9 So at the time, they had this one responder -- they had this one
10 responder. They were thinking it was PDL-1. They were not thinking
11 that it was MSI-high. This is what they were focused on. And that's
12 another factor that you need to take into account when you're thinking
13 about reasonable expectation of success.

14 JUDGE KATZ: But if we look in 2015 though, we have the
15 MSR as prior art, and we have this article as prior art. So if you put
16 the two of them together, the MSR tells you to sort of look at MSI as a
17 possibility, and then you have this paper, which does identify a patient
18 who is MSI-H, who it's successful in.

19 And so how -- if you combine the two in 2015, how does that --
20 can you comment on the reasonable expectation of success in 2015,
21 not at the time that -- which is I guess 2012 at the time, that the
22 Lipson paper was published.

23 MS. BROWN-MARSHALL: So I would say in 2015, this
24 would still fall into that category of hope, right, because it's one
25 patient.

1 JUDGE KATZ: Right.

2 MS. BROWN-MARSHALL: It's still anecdotal. They're MSI-
3 high, you know, maybe that that's motivation to look into it.
4 Motivation to pursue. But, remember, that's not reasonable
5 expectation of success. Reasonable expectation of success is
6 reasonable expectation of success in the claimed method. And that
7 does not get you to reasonable expectation of success that this method
8 of MSI-high can be a treatment selection marker.

9 JUDGE KATZ: Okay.

10 MS. BROWN-MARSHALL: I'd like to quickly move on to
11 objective indicia. And I think for my colleague, Ms. McCormick is
12 going to be presenting the specific objective indicia arguments, but I
13 would just like to touch on nexus because that seems to be sort of the
14 crux of Merck's argument against this.

15 JHU has presented evidence that there is a nexus between the
16 evidence of objective indicia and the claim method two different
17 ways, the first of which is the presumption -- that there's a
18 presumption because the asserted objective indicia evidence is tied to
19 the specific product, which is Merck's Keytruda product, with the
20 indications on its label specifically for treating MSI-high colorectal
21 cancer, and that that product is disclosed and claimed in the patent.

22 We believe we have presented evidence of presumption. The
23 only rebuttal they have to that is attorney argument. They have not
24 presented any evidence that we should not be entitled to that
25 presumption of nexus.

1 Even if they had, we can still -- even if there is no presumption,
2 we can still prove nexus by showing that the evidence of secondary
3 considerations is the direct result of the unique characteristics of the
4 claimed invention. As counsel pointed out, this was -- there's only
5 two limitations in this claimed method and the independent claims,
6 that it's testing for MSI-high, and if the patient, the colorectal cancer
7 patient is MSI-high, treat them. If they're not, don't.

8 JUDGE KATZ: So if we were to find that there -- that the
9 claim -- the independent claims are anticipated, you're showing of
10 commercial success in the secondary -- all the other considerations --
11 secondary considerations are relevant to the independent claims. Not
12 to the limitation -- the added limitations of the dependent claims. Is
13 that correct?

14 MS. BROWN-MARSHALL: No, Your Honor, that's not
15 correct --

16 JUDGE KATZ: Okay.

17 MS. BROWN-MARSHALL: -- because the -- if we look at the
18 indication -- so if I could get slide 81. So there's two indications.
19 Indication 1.8 is for colorectal cancer patients who received prior
20 treatment. So that goes to one of the -- one of the dependent claims
21 where it talks about the patient has received prior therapy and
22 progressed on the prior therapy. So there are -- the indications on
23 Merck's label also line up with the dependent claims of the 393 patent.

24 JUDGE KATZ: But then the -- okay. So you're relying on the
25 presumption. You're not showing that there was any particular

1 commercial success in those patients who hadn't received any prior
2 therapy?

3 MS. BROWN-MARSHALL: So our commercial success
4 analysis looks at MSI-high colorectal cancer patients as a group. It
5 doesn't distinguish between the two embodiments. One embodiment
6 is has received a prior therapy, and the indication 1.9 is an
7 embodiment where they have not received a prior therapy.

8 JUDGE KATZ: Right. So you're just relying on the
9 presumption of the has not or -- which is a -- has received the prior --
10 has not received a prior therapy when you say that it lines up with the
11 label. Sorry, I'm not being very clear. I think I've answered my
12 question.

13 MS. BROWN-MARSHALL: Okay.

14 JUDGE KATZ: Okay. Thank you.

15 MS. BROWN-MARSHALL: I would say that both would
16 apply. So certain indications are related to certain dependent claims
17 and certain indications are related to other dependent claims. We
18 have to look at a claim by claim basis. But they all meet the
19 requirements of nexus.

20 JUDGE KATZ: Okay. Thank you.

21 MS. BROWN-MARSHALL: And just to touch on a few points
22 that Merck highlighted in talking about the nexus between the
23 evidence of objective indicia and the claim method. So Merck, in its
24 slides 86 and 87, focuses on JHU's evidence from 2012 and 2013. But
25 that ignores a lot of evidence that comes later.

1 It ignores the fact that Dr. Le, when she presented the results at
2 the ASCO conference, which Dr. Neugut, Merck's expert, referred to
3 as the Super Bowl of cancer conferences, was presented to giant
4 fanfare. She got what she called a movie premier treatment. She got
5 interviewed. There was a press release. The results, the preliminary
6 results of the clinical trial were published in the New England Journal
7 of Medicine.

8 And that evidence goes beyond just the critical date, too. After
9 the critical date, the FDA granted Merck breakthrough therapy
10 designation for those indications for MSI-high colorectal cancer.
11 FDA approved treating MSI-high colorectal cancer in 2017. My
12 colleague, Ms. McCormick, is going to touch on some other evidence
13 related to long-felt need commercial success that came after that
14 critical date.

15 So just saying that JHU is just focusing on that 2012 to 2013
16 date is inappropriate because that's not where we are focusing. We
17 are focusing on the totality of the objective indicia evidence. And that
18 is where the proper scope. Thank you.

19 JUDGE KATZ: If you could give us a warning when you're
20 coming up on the portion where you want to close the livestream.

21 MS. MCCORMICK: Yes, Your Honor. I will do that. I'm
22 going to address the non-confidential objective indicia first, and then
23 do the confidential ones together at the end.

24 JUDGE KATZ: Okay. And we have about 14 minutes left on
25 the --

1 MS. MCCORMICK: For the 90 minutes, but then we have an
2 additional 15.

3 JUDGE KATZ: No. That was including the 15. So there
4 was -- because you --

5 MS. MCCORMICK: You put --

6 JUDGE KATZ: Okay. No.

7 MS. MCCORMICK: I'm sorry.

8 JUDGE KATZ: That's right. That's right.

9 MS. MCCORMICK: You put --

10 (Simultaneous speaking)

11 JUDGE KATZ: So there is about 25 including the 10 minutes
12 for the confidential portion. Okay.

13 JUDGE SNEDDEN: But we also have five minutes rebuttal.

14 MS. MCCORMICK: Right.

15 JUDGE KATZ: Right.

16 JUDGE SNEDDEN: Right.

17 MS. MCCORMICK: All to say, I'll try to move quickly. May
18 it please the Board, Madelyn McCormick on behalf of Patent Owner
19 Johns Hopkins. And I'm going to present on Patent Owner's -- if I
20 could have slide 91 please -- Patent Owner's common sense and real
21 world facts of objective indicia, which are important here as the
22 Federal Circuit says to help guard against slipping into use of
23 hindsight and help resist the temptation to read into the prior art
24 teachings of the invention, which is what Merck is doing here.

1 So starting with unexpected results at slide 98, and my
2 colleague did talk about unexpected results in the context of a
3 reasonable expectation of success, but it's important here, too, as a real
4 world fact showing non-obviousness.

5 So on slide 99, we can see that the expectation at the time of
6 invention was failure. We had two studies run on colorectal cancer
7 patients using a PD-1 inhibitor that resulted in 97 percent and 95
8 percent failure rates. And after the invention, we have study results
9 showing a failure rate that got turned on its head. That the results
10 were unheard of. And we went from a 3 percent success rate to a 90
11 percent success rate, which we can see here on slide 99 in the row
12 second from the bottom.

13 So now Merck claims that these results were expected. But that
14 can't be true in the face of Patent Owner's evidence to the contrary.
15 And even Petitioner's clinician, Dr. Neugut, admits that the survival
16 benefit here of Hopkins' invention is impressive.

17 So in slide 100, we also have evidence from 2017, this article
18 exhibit 21 is from 2017 where the inventors were reflecting on their
19 invention. And we have first Dr. Drew Pardoll, an invention on the
20 393 -- an inventor on the 393 patent telling another inventor that
21 checkpoint inhibitors didn't seem to be working in colorectal cancer.
22 And only after getting the results from the MSI-high study did the
23 inventors see tumors melting away.

24 And Dr. D, as a clinician, and also an inventor on the 393
25 patent said in the bottom left on slide 100, "Things don't work a lot.

1 When something works, it's unbelievable." And that's exactly what
2 these results were here. Not expected. Wholly unexpected.

3 And in slide 100, we have another inventor, a clinician, Dr. Le,
4 who my colleague talked about for you. An experienced clinician
5 seeing how the MSI-high colorectal cancer patients responded so
6 dramatically. And that that, indeed, was miraculous in her experience
7 because in her experience she had not seen such remarkable response
8 to any treatment during her career to date.

9 And we don't need to rely just on the inventors, although they
10 are experienced clinicians themselves. We can turn to slide 102 and
11 see Hopkins' expert highlighting that if the results had been obvious, it
12 would have been unethical to run the study testing the MSS patients
13 against the MSI-high patients. So these results could not have been
14 obvious because we had to run the study. It was an experiment.

15 And on slide 103, we can see from the Federal Circuit why this
16 is important, "Unexpected results are useful to show the improved
17 properties provided by the claimed inventions are much greater than
18 would have been predicated." And here, again, we went from a 3
19 percent response rate in colorectal cancer patients to a 90 percent
20 response rate once it was determined that treating colorectal cancer
21 patients in response to their MSI-high status resulted in this 90 percent
22 success rate.

23 Okay. The next factor to touch on here is industry praise,
24 which we can see at slide 104. And Patent Owner presents industry
25 praise from the oncology community, from FDA, and from Petitioner,

1 Merck, themselves. So from the Federal Circuit, we understand that
2 this evidence is important because industry participants are unlikely to
3 praise an obvious advance over the known art.

4 So my colleague already touched on what happened when the
5 inventors first publicly disclosed their results, but on slide 105, we can
6 see where Petitioner presented this during this trial. Dr. Le presented
7 her results during ASCO, the Super Bowl of the oncology community
8 as characterized by Merck's own declarant. And that when she
9 revealed her data to a huge room of attendees, you could hear a pin
10 drop. Now it seems unlikely that the oncology community is going to
11 stand -- in the standing room only be silent if the results are obvious.

12 So where the results were published is also evidence of industry
13 praise. The results were published in the New England Journal of
14 Medicine, which Merck's declarant characterized as the most
15 prestigious journal with the most prominent papers that are published
16 in medicine. And here we have Merck's own words to rely on for
17 industry praise as well. Slide 109.

18 We have a press release from Merck in 2015 calling these
19 exciting results, while early, suggest the evidence of DNA mismatch
20 repair deficiency may be an important way of identifying tumors that
21 are responsive to checkpoint blockade. So even in 2015, Merck is
22 saying it's exciting. Merck is also saying -- using language like may
23 to say that they're still not sure, and that these findings were early.

24 And then moving down the timeline, slide 110. Patent Owner's
25 results, even in 2017 were published in Science, which is a well-

1 respected journal. So even 10 years later, it's clear that the industry
2 still valued these results. And here we can see on slide 110, that in
3 2017, the results from the MSI-high study were being characterized as
4 a proof of concept study, again, emphasizing that this was an
5 experiment that they didn't know how it would go.

6 And on slide 111, again, in 2017, we have Merck's own words
7 to rely on crediting Johns Hopkins for their important scientific work
8 in this field of identifying MSI-high as a biomarker for treating cancer
9 patients. And on slide 113, we can see Petitioner's clinician
10 recognizing how JHU's invention changed the standard of care.

11 We have Dr. Neugut explaining that after the results of
12 Hopkins' invention, and after Pembrolizumab was approved for
13 treatment of MSI-high colorectal cancer patients, he changed his
14 standard of care. Not just him. All oncologists did that, and because
15 of -- he did that because of the obvious efficacy of the drug in that
16 context.

17 And then, finally, on slide 114, we have, again, from 2018, so
18 three years after the invention, we have another article highlighting
19 that this invention was a paradigm shift and a tipping point in the
20 treatment of colorectal cancer patients. Okay.

21 And then, finally, for the non-confidential portion, we have
22 skepticism, slide 120. The Federal Circuit tells us this is an important
23 factor in rebutting hindsight bias because expressions of disbelief by
24 experts constitute strong evidence of non-obviousness.

1 And I just want to note that skepticism here, the evidence we're
2 presenting does seem to dovetail and overlap with a reasonable
3 expectation of success. First, on slide 120, we have Patent Owner's
4 declarant, Dr. Lonberg, who was a BMS employee has firsthand
5 knowledge of BMS's skepticism of whether treating MSI-high
6 colorectal cancer patients in response to their MSI-high status was
7 going to work.

8 He states -- you can see on the second line here on slide 120
9 that the study was very risky, and BMS passed on participating in this
10 study multiple times. But we don't have to rely -- the Board doesn't
11 need to just rely on that. We can look at Merck's own words.

12 Again, on slide 122, this is from that same 2017 article where
13 the inventors are reflecting on their invention. We have Merck's VP
14 of global clinical oncology commenting that early on there had been
15 prior small numbers of colon cancer patients who had been treated
16 with anti-PD-1 agents, and the responses were pretty much zero. So
17 they idea was early on that it really wasn't going to work in colon
18 cancer as a monotherapy.

19 So those are Merck's own words saying that this wasn't going
20 to work. They thought it wasn't going to work. And I think further
21 evidence of Merck's skepticism on slide 123 to set the stage here for
22 this, at the time before the invention, Merck did not want to wake up
23 in five years and wish they had blew another billion dollars on this
24 drug. And when considering which potential Keytruda clinical studies

1 they wanted to run, Mr. Perlmutter reportedly responded, "There is no
2 line. Do all of them."

3 And what did Merck do when Hopkins asked them to fund their
4 study on slide 124. They said no. We'll give you the drug. You do it
5 yourself. And this is reflected in the record at Exhibit 2131 that at the
6 time of the study was going to be run, Merck was going to provide no
7 funding.

8 Now to respond to what I think Petitioner might argue on this,
9 that Dr. Le said in -- that Dr. Le somehow undermined this evidence
10 of skepticism on Merck's part. She said in her declaration that, yeah,
11 eventually Merck agreed to provide funding, but only after they saw
12 initial results. She didn't remember the exact timing, but she did
13 remember that they were going to do it, but only after seeing the
14 initial results. And that's the end of the open portion.

15 JUDGE KATZ: Okay. All right. Then we will close the
16 stream and ask those who should not be hearing to exit the room.

17 MR. RATLIFF: Your Honor, is it possible for us to have like a
18 five-minute --

19 JUDGE KATZ: Yes.

20 MR. RATLIFF: -- bio break?

21 JUDGE KATZ: Yes. Yes, there is. So we will reconvene at
22 4:10. At 4:10?

23 (Simultaneous speaking)

24 UNIDENTIFIED FEMALE PARTICIPANT: -- Your Honor.

25 JUDGE KATZ: Okay. Thank you. We'll take everything.

1 (Whereupon, the above-entitled matter went off the record at
2 4:3 p.m., and resumed at 4:13 p.m.)

3 THE CLERK: All rise.

4 JUDGE KATZ: Okay. Have a seat. Okay. So -- let's just
5 make sure. Okay. Let me just get confirmation that the line is still
6 closed.

7 MS. MCCORMICK: Thank you, Your Honor.

8 JUDGE KATZ: Okay. We do have confirmation, and there are
9 15 minutes left.

10 MS. MCCORMICK: That's my understanding.

11 JUDGE KATZ: Good.

12 MS. MCCORMICK: I'll take more.

13 JUDGE KATZ: Okay. Please begin.

14 MS. MCCORMICK: Thank you, Your Honor. So continuing
15 with the objective indicia of non-obviousness of the 393 patent
16 claims, we have evidence of long-felt but unmet need. And this is
17 important because an obviousness analysis -- to an obviousness
18 analysis because the idea is that a need would not have persisted if
19 the answer was obvious. And here, JHU's solution to this need was
20 not obvious.

21 So on slide 92, to set the stage here, before JHU's invention,
22 metastatic colorectal cancer had an overall survival rate of less than
23 two years. And for colorectal cancer patients who failed two
24 treatments, the best available treatment at the time improved life
25 expectancy by only one to two months. And this was considered a

1 significant amount of time for those patients, and that kind of
2 treatment was quickly adopted into practice. And the MSI-high
3 colorectal cancer patients fared no better.

4 So in his declaration, Dr. Goldberg explained that MSI-high
5 colorectal cancer was a death sentence before JHU's invention. And
6 particularly, with patients with advanced disease, a cure was unheard
7 of. But JHU's invention is the only time that Dr. Goldberg has seen a
8 cure for those patients in his 35 years of practicing oncology.

9 And here, again, the Board does not need to rely on Dr.
10 Goldberg alone. On slide 93, we can see that Merck, Petitioner, told
11 FDA of this long-felt, but unmet need for MSI-high colorectal cancer
12 patients. And this evidence is from 2015. In Merck's own words to
13 the FDA, there was an unmet medical need. The prognosis for a
14 patients with metastatic MSI-high colorectal cancer is poor in part due
15 to a lack of treat tailored to take advantage of this unique biology.
16 Therefore, metastatic MSI-high colorectal cancer patients represent a
17 group of patients with high unmet medical need.

18 And Merck made this representation to FDA more than once.
19 We can see on slide 94, again, Merck is telling FDA of the urgency to
20 make Pembrolizumab available to end-stage MSI-high colorectal
21 cancer patients. The need here and the long felt need is clear from
22 Merck's words alone.

23 And FDA themselves agreed there was an unmet need. We can
24 turn to slide 95. Here FDA granted a breakthrough therapy
25 designation for this treatment of MSI-high metastatic colorectal

1 cancer patients where FDA gives this breakthrough therapy
2 designation to drugs for treatment of serious conditions where there is
3 an unmet medical need. So we have an expert clinical oncologist,
4 Merck, and FDA all agreeing there was an unmet medical need for
5 treatments for MSI-high colorectal cancer patients. But there's even
6 more.

7 So during the course of this trial, Merck's own clinician, Dr.
8 Oberstein on slide 97, agreed that, in his own words, as of July 10th,
9 2015, MSI-high colorectal cancer patients did qualify as a high unmet
10 need. This was one of Merck's clinicians agreeing.

11 We have the other clinician agreeing, Dr. Neugut with 40 years
12 of experience adding a little more color too that before JHU's
13 invention, curing a patient with a metastatic solid tumor was a very
14 rare phenomenon. And in his career, which stretched back 40 years,
15 and encompassed treating thousands of patients, he cured seven. So
16 after JHU's invention, as embodied by Keytruda, he's probably cured
17 another seven in just the last five years.

18 And Dr. Neugut's experience here aligns with Patent Owner's
19 expert Dr. Goldberg in curing patients never before thought possible
20 using JHU's claimed method. So it's clear here that not only was there
21 a long-felt, but unmet need based on JHU's experts' opinion, Merck's
22 clinicians, Merck themselves, and FDA agreeing to this.

23 We also have here evidence that JHU's invention met that need
24 with the claimed invention of the 393 patent. So if we could turn to

1 slide 115 to look at commercial success of the embodiment of JHU's
2 patented claims.

3 So commercial success is relevant here because the law
4 presumes an idea would have successfully been brought to market
5 sooner in response to market forces had the idea been obvious. The
6 idea being if you're going to -- if the end goal is that you're going to
7 make a lot of money, a lot of people are going to try to do it.

8 So we can look here at some of the economic factors proving
9 the commercial success of JHU's invention. On slide 116, we have
10 evidence of Keytruda sales for just the MSI-high colorectal cancer
11 patients being treated with Keytruda, sales that embody the claimed
12 invention.

13 So just to touch on nexus here for a moment, this is the unusual
14 case where we have complete co-extensiveness with the evidence of
15 commercial success here and the claimed invention. To make sales of
16 Keytruda for MSI-high colorectal cancer patients, you have to practice
17 the claimed invention, and that practice of the claimed invention is on
18 the label for Keytruda. The two steps of the claimed invention are
19 what are on the label for Keytruda.

20 So getting back to the commercial success here, we have both
21 experts agreeing that sales for MSI-high colorectal cancer patients
22 from 2017 to 2023 totaled [REDACTED]. And evidence of sales alone is
23 enough to support a commercial success objective indicia here. And
24 that's from the Federal Circuit. We also have the growth in the

1 number of patients also being evidence of commercial success here in
2 2017 starting off with [REDACTED] in 2023.

3 Okay. So next on slide 117, we have, you know, Merck tries to
4 fault Hopkins for not considering brand or halo effect. Various things
5 that Merck itself doesn't analyze in the context of commercial success.
6 But Merck had [REDACTED] for colorectal cancer patient before 2017,
7 and after they have over [REDACTED]. And those sales would not have
8 been possible expect for practicing the claimed invention, which is
9 here on slide 117 from Hopkins' declarant Dr. Goldberg.

10 And, again, we don't need to rely on Dr. Goldberg alone. On
11 slide 118, we can see from Merck's own sales data that before 2017,
12 [REDACTED] for colorectal cancer patients before it was
13 approved -- before that indication was on the Keytruda label. And
14 Merck's other criticisms of this commercial success also ring hollow.

15 So counsel for Petitioner brought up blocking patents, the
16 Federal Circuit instructs that the mere existence or sheer number of
17 purported blocking patents, there's not a lot of analysis to show that
18 these were blocking anyone from developing the claimed invention,
19 those blocking patents do not without more necessarily detract from
20 evidence of commercial success of a product. And here we have clear
21 evidence of commercial success in that [REDACTED] figure.

22 So we also have no explanation from Merck on why third
23 parties such as Hopkins would have been deterred from developing
24 the claimed method. Indeed, they weren't. This is not the common
25 situation where blocking patents are relevant.

1 For instance, in the case Merck cites -- actually Merck case,
2 Merck itself had blocking patents, and then had the claimed invention
3 that was at issue. So here, Hopkins was not blocked from developing
4 this claimed invention. Nor, was Merck blocked from
5 commercializing it.

6 So in sum, slide 125, we can see these five categories of
7 objective indicia to show the non-obviousness of the 393 patent
8 claims that must be considered at the same time as evaluating
9 obviousness. Unless the Board has any questions, I reserve the rest of
10 the time for rebuttal.

11 JUDGE KATZ: Okay. Thank you. Okay. All right. So for
12 Petitioner, you'll start with -- sorry. Petitioner. And you have 30
13 minutes for rebuttal.

14 MS. STAURING: I believe we might have 45. I think that's
15 the time that we were -- we left off at I believe --

16 JUDGE KATZ: Okay.

17 MS. STAURING: -- 59 minutes.

18 JUDGE KATZ: Oh, because you reserved. Okay. Okay.

19 MS. STAURING: And, Your Honors, before we get started, I
20 don't believe that any portion of our rebuttal needs to be maintained
21 under seal --

22 JUDGE KATZ: No.

23 MS. STAURING: -- or have the record closed.

24 JUDGE KATZ: Okay. All right. Then let me just -- moving
25 things back up. Is there anybody waiting outside?

1 :

2 MS. BROWN-MARSHALL: Yes, there is, Your Honor.

3 JUDGE KATZ: Okay.

4 MS. BROWN-MARSHALL: May I grab --

5 JUDGE KATZ: Sure. Okay. Okay. Are we ready? Thank
6 you.

7 MS. STAURING: Thank you, Your Honors. May it please the
8 Board. Your Honors, I'll address JHU's arguments on secondary
9 considerations here, and my colleague, Mr. Ratliff, will address
10 anticipation and obviousness more generally on rebuttal. Can we
11 please bring up Petitioner's slide 87?

12 Before turning to the specific secondary considerations at issue
13 here, Your Honors, I want to just turn back and highlight this timing
14 point once more because this really emphasizes why JHU's focus on
15 this 2012, 2013 timeframe isn't sufficient to carry any weight for its
16 evidence here because during those intervening years, in addition to
17 the method of treating a MSI-high colorectal cancer patient with
18 Pembrolizumab that published in the MSR, additional art published,
19 and that included the prior successful treatment of the MSI-high CRC
20 patient with another PD-1 inhibitor that JHU's counsel discussed as
21 shown in Exhibit 1057, but that was also discussed in another exhibit.

22 And that's an article by Kim that published in November of
23 2014, and that's Exhibit 1038. And in that publication, Kim discusses
24 that this early report of a complete response based on that observation
25 and others, it's been hypothesized that MSI-high tumors are more

1 susceptible to immune response and attack, and talked about the other
2 clinical trial that was ongoing at the time that JHU's declarant Dr.
3 Lonberg refers to as a contemporary study to treat MSI-high
4 colorectal cancer patients with another PD-1 inhibitor.

5 And so as you can see here on slide 87, there is all of these
6 teachings in the prior art that are saying that MSI-high colorectal
7 cancer patients are likely to benefit from treatments with
8 immunotherapy that includes PD-1 inhibitors and Pembrolizumab.
9 And the MSR and additional clinical studies were announced to treat
10 such patients with Pembrolizumab and PD-1 inhibitors. And so this
11 focus on the 2012, 2013 timeframe to allege skepticism, and unmet
12 need, and unexpectedness should carry very little weight in the light
13 of the evidence that existed as of the alleged invention date.

14 And if we can turn to slide 93 please. I'd also like to address
15 the nexus point. Your Honors, there is no co-extensiveness here.
16 JHU's counsel stated that the claims here require treatment -- a
17 treatment based on determining the patient's tumor is MSI-high. But
18 there is no evidence in the record to show that a doctor prescribing
19 Keytruda according to the Keytruda labeling treats a patient based on
20 the determination that the patient is MSI-high as opposed to other
21 reasons that are entirely tied to the drug itself, its brand recognition,
22 and the safety of that drug.

23 And the co-extensiveness requirement the Federal Circuit has
24 explained cannot be reduced to simply what JHU's counsel asks for
25 here, which is the patent claims broadly covering the thing that's

1 alleged to have co-extensiveness. In the cases that JHU cites, all of
2 those cases deal with a product, but the Federal Circuit has made plain
3 that co-extensiveness -- the inquiry for co-extensiveness cannot be
4 reduced to just do the patent claims broadly cover the product.

5 And that would be true here for the use of the drug according to
6 its labeling. It's not enough to satisfy the co-extensiveness
7 requirement for the patent claims to broadly cover such a use. And
8 we would, of course, dispute that even a doctor following the labeling
9 practices those claims.

10 On nexus and fact, JHU raises a new argument today because
11 we don't see anywhere in their papers any tie between secondary
12 considerations and specific dependent claims. And JHU doesn't even
13 allege novelty of the additional limitations for certain dependent
14 claims.

15 And my colleague, Mr. Ratliff, highlighted that our slides 71
16 through 81 show how JHU does not contest that those additional
17 limitations were known in the prior art. It appears we might have lost
18 connection. Can we go to slide 93 please? Thanks.

19 So turning to skepticism in particular here, all of the evidence
20 in the record shows a lack of skepticism. Other than JHU's declarant
21 Dr. Lonberg, there is no evidence in the record that shows that there
22 wasn't a belief that MSI-high colorectal cancer patients would benefit
23 from the treatment of Pembrolizumab. And JHU's allegations that
24 Merck or others in the industry were skeptical as of July 10th, 2015

1 fall flat because the MSR identified Merck as a collaborator, and that
2 published in June of 2013.

3 Exhibit 1053 also published prior to the alleged invention date
4 and reflects a study by BMS to treat MSI-high colorectal cancer
5 patients with its PD-1 inhibitor. JHU alleges skepticism by BMS, but
6 all that we know is that BMS did not want to pursue the study with
7 JHU in 2012. We don't know why, but JHU went -- excuse me --
8 BMS did go on to do its own study to treat MSI-high colorectal cancer
9 patients with its PD-1 inhibitor, and that can't support a finding of
10 skepticism as of July 10th, 2015.

11 JHU also showed Your Honors a slide today, and that's JHU
12 slide 122. Can we bring that up please? And JHU said that this slide
13 evidenced -- admitted skepticism by Merck's Dr. Eric Rubin. But
14 when you look at the context of page 17 of Exhibit 2121, you see that
15 this discussion comes after speaking about the highly compelling
16 reasons to pursue treating MSI-high colorectal cancer patients with
17 Pembrolizumab.

18 And this statement was talking about early on, meaning prior to
19 much of the relevant evidence here including the prior successful
20 treatment of an MSI-high colorectal cancer patient with another PD-1
21 inhibitor. And if we look at page 17 of Exhibit 2121, you see earlier
22 in the document repeated references by Dr. Rubin to this particular
23 MSI-high study being one that Merck wanted to support because of
24 the, quote, "Compelling scientific rationale."

1 And he was asked, you know, this was during a time period
2 prior to Keytruda's approval when there was probably a fairly limited
3 amount of drug supply, and Dr. Rubin said that's right, but as I
4 mentioned, this had a compelling scientific rationale, and was based
5 on really good science. And so that's Dr. Rubin speaking about why
6 Merck wanted to pursue such a study. And Merck did pursue that
7 study and collaborated with JHU in 2013, more than two years before
8 the alleged invention date here. And if we can turn to slide 96 please.

9 JHU also talks about funding throughout many of its secondary
10 considerations allegations, and we disagree that this question of
11 financial support for the MSI-high study has bearing on skepticism or
12 unexpectedness in view of the other evidence that's in the record. But
13 it's important to highlight because JHU presents a misleading picture
14 because its own declarant Dr. Le admitted that, not only did Merck
15 provide drug for the, but Merck provided funding.

16 And when you look at Exhibit 2183, if we can bring that up,
17 this is an exhibit that JHU relies upon to say that Merck declined
18 funding. But no evidence in the record actually reflects Merck
19 declining funding. All of the evidence shows that JHU came to
20 Merck and said they were in the fortunate position to have funding
21 available from a non-profit source and would welcome support for
22 Merck in addition to supply of the drug.

23 And Merck absolutely did supply support for this study. It's not
24 disputed that Merck personnel provided the dose and the scanning
25 frequency that patients should have their tumors measured in

1 development of the study protocol. It's not disputed that Merck
2 personnel were involved in the analysis and collection of the data
3 including to submit on Merck's -- it was Merck's requirement to
4 submit such information to the FDA. And that Merck personnel were
5 involved with all of that.

6 And if we go back to slide 93, the record evidence here reflects
7 that Merck was a collaborator in this study. And so allegations of
8 Merck being skeptical as of July 2015, they just don't make sense.

9 Before we turn to long felt, unmet need, I also just want to
10 address this timeline slide, slide 89 of JHU's that we spoke about
11 earlier because this relates to the funding discussion. So if we can
12 pull up slide 89, and this is the redacted version. And I'd like to
13 respect the fact that we're on the public line, so I'll just refer to this
14 information at a high level without getting into the details.

15 But if Your Honors looks at the confidential version of this
16 document, you'll see a time marker in 2016 that JHU alleges supports
17 its financial arguments in this case. And we think that's entirely
18 improper for JHU to include such a time marker because it's entirely
19 tied to Exhibit 2410 that Your Honors expunged from the record, and
20 said would not be considered. JHU cites to Dr. Oberstein's deposition
21 testimony there, but when you look at that portion of his testimony,
22 it's just talking about Exhibit 2410.

23 And so we think the inclusion of this argument is entirely
24 improper in view of the Board's March 3rd, 2025 order. But even if
25 Your Honors considers this time marker event, it's just false because

1 as we identified in -- which is Board Exhibit 3009, our email to the
2 Board, we identified inconsistent evidence with the position that JHU
3 puts forth on this slide, and that's not included here. And so we just
4 note that while we don't even believe this funding dispute and the
5 timing of financial payments is relevant to the questions of skepticism
6 and unexpectedness here, this is a misleading argument from JHU.
7 We can turn to slide 94 please.

8 Finally, on skepticism, JHU's own declarant Dr. Lonberg
9 admitted that even prior to the MSR's posting, he was enthusiastic
10 about the study described by the MSR. So JHU's arguments that
11 Merck, others in the industry, and even their own purported expert
12 were skeptical as of the alleged invention date here just don't make
13 sense, and should carry very little weight in the Board's assessment of
14 secondary consideration. Can we bring up slide 99 please?

15 The evidence here similarly shows that no long-felt, unmet
16 need existed for treating MSI-high colorectal cancer patients with
17 Pembrolizumab by July 10th, 2015. And JHU's counsel today
18 highlighted its nexus problem because they're trying to tie the unmet
19 need to colorectal cancer generally. But the specific method of
20 treatment that's claimed here is a method of treating a patient
21 determined to be MSI-high in response to that determination.

22 And there is no unmet need as of July 10th, 2015 because as
23 Merck's declarant Dr. Oberstein testified, the MSI-high study record
24 was in the prior art, a number of other prior art references
25 independently urged the MSR's treatment method. And another study

1 of another PD-1 inhibitor was announced and ongoing as of the
2 alleged invention date, and another Merck study to treat MSI-high
3 colorectal cancer patients with Pembrolizumab was announced prior
4 to the alleged invention date. So to the extent any need existed here, it
5 was not unmet.

6 And if we turn to slide 100, we can see that to the extent any
7 need existed here, it was not long-felt because as JHU's own
8 declarant, Dr. Goldberg, testified, after the first breakthrough had
9 occurred with Nivolumab in 2010, there was intense interest on the
10 parts of oncologists and pharmaceutical companies alike to test PD-1
11 inhibitors and treat cancer patients that would have that -- would
12 realize their potential benefit. And so to the extent any need existed,
13 it was not unmet, and it was not long felt.

14 And JHU's arguments that are in connection with its slides 93 to
15 97, which I won't pull up because they do contain highly confidential
16 information, you'll see on its timeline slide that the events connected
17 to those slides come after the alleged invention date here. And that's
18 because all of those statements and arguments are tied to a need for an
19 FDA approved product in a certain patient population. Not the
20 specific method of treatment that's claimed here.

21 And there is no requirement under the law that JHU has cited,
22 or that we're aware of for a method of treatment to be considered
23 unmet until the time that there is an FDA-approved product for that
24 treatment method. And so JHU's evidence of long-felt, unmet need
25 carries very little weight here as well.

1 We turn to slide 102. With respect to unexpected results, all of
2 the evidence in the record here shows that it was expected that MSI-
3 high colorectal cancer patients would benefit from treatment with
4 Pembrolizumab. JHU's counsel today, and in its papers, allege that
5 there was no expectation of success because it would have been
6 unethical to treat MSI-stable patients.

7 But that focuses the question incorrectly, and JHU's own
8 declarant, Dr. Goldberg, conceded that it would be ethical to conduct
9 such a study even though it was believed that the MSI-high patients
10 would respond better than the MSS patients. And that can be found in
11 his deposition transcript, which is Exhibit 1136 at page 175, line 17
12 through page 176, line 8. And that's cited in our reply at page 22.

13 As Merck's declarant, Dr. Oberstein, testified, the MSI-high
14 study was actually already being conducted. BMS was conducting its
15 own study of its PD-1 inhibitor. Merck had initiated another trial to
16 treat MSI-high colorectal cancer patients with Pembro. And there
17 were many teachings in the prior art that encouraged this treatment,
18 and said that MSI-high patients were likely to benefit. There's no
19 evidence in the record here that there was a belief that those patients
20 would not benefit.

21 If we turn to slide 104. With respect to commercial success, the
22 393 patent claims here are simple, and Your Honors can take a look at
23 the patents that are in the record and that are discussed by Merck's
24 declarant Dr. Sheridan. He discusses the preventative effect that the

1 blocking patents in the record here would have had on others' entry
2 into the market to develop a method of treatment using Merck's drug.

3 And in particular, if Your Honors take a look at Exhibit 1238,
4 and that's at line 7 -- or column 7, lines 52 to 59, and column 21, lines
5 65 through column 22, line 30. You'll see the disclosures of Merck's
6 drug as well its use to treat cancer broadly. And the effect of these
7 blocking patents reduces any evidence of commercial success here as
8 well as long-felt, unmet need.

9 JHU's argument that others were not blocked from developing
10 in this space because the 393 patent itself exists just doesn't make
11 sense because JHU only had access to Merck's drug because the
12 parties were engaged in a collaboration pursuant to a contract that
13 provided JHU with access to Merck's drug. So that argument does
14 nothing to undercut the effect of blocking patents in this case. And
15 Dr. Sheridan also discusses throughout his declaration several other
16 reasons that commercial success evidence should be afforded little
17 weight here.

18 Finally, on slide 107, with respect to industry praise, again,
19 JHU cannot establish nexus here between its purported evidence and
20 the specific method of treatment claimed. If JHU's alleged evidence
21 of industry praise has nexus to anything here, it's to Merck's drug and
22 its inherent properties that have led to the benefit of cancer patients
23 across many different tumor types.

24 Unless Your Honors have any questions, for the reasons
25 discussed here today and in our papers, the Board should afford little

1 to no weight to JHU's allegations of secondary considerations here.
2 And any weight that the Board does afford to secondary
3 considerations is nevertheless outweighed by the strong evidence of
4 obviousness that is in the record here.

5 I'd like to turn the remainder of my time over to my colleague,
6 Mr. Ratliff unless Your Honors have any questions. Thank you.

7 JUDGE KATZ: Thank you.

8 MR. RATLIFF: Your Honors, in JHU's presentation, there was
9 lots of confusion. I want to start off with a couple things. First of all,
10 this is not about whether or not the treatment method works or the
11 degree in which it works. This is a situation where the two-step
12 treatment method that was claimed was disclosed in the prior art. So
13 this is about disclosure, and that disclosure was more than two years
14 before JHU's alleged invention date.

15 And make no mistake, when JHU talks about the MSR, and
16 they say it's an invitation to investigate, it's plainly not. If we can
17 bring up our slide 22, this is serious. This is a clinical study record
18 that's been posted. Posted in part to solicit patients, critically ill
19 cancer patients for treatment. And when you look at the title of the
20 study, something like that, it's a phase II study focusing on a specific
21 type of patient. This is by no means an invitation to investigate.

22 And on this point about the treatment method and it's all about
23 disclosure, if we go back and just think to the Schering case, that had
24 nothing to do -- there was no knowledge about the metabolite. So it
25 would sound impressive if in Schering they were talking about how

1 great the metabolite was. But that's not the situation, how great the
2 treatment method is because the treatment method was disclosed.

3 Now on this invitation to investigate and what we see posted
4 here, the MSR, JHU comes before Your Honors, and we heard it
5 several times that they said we don't know what's going to happen.

6 Failures in the art. It's going to fail. We're not really sure. [REDACTED]
7 [REDACTED]

8 [REDACTED], and that's Exhibit 1116 at 2, 18, 19, 39, and 40. And
9 when you look at -- when you look at Dr. Oberstein's declaration, at
10 Exhibit 1150 --

11 MS. BROWN-MARSHALL: Yeah.

12 JUDGE KATZ: I'm sorry, counsel.

13 MS. BROWN-MARSHALL: I'd like to object. So the IND
14 submissions are confidential information --

15 JUDGE KATZ: Mr. Ratliff.

16 MS. BROWN-MARSHALL: -- which should not be discussed
17 in --

18 (Simultaneous speaking)

19 JUDGE KATZ: Are they -- what was -- the exhibit number
20 was 11?

21 MR. RATLIFF: 1116. The IND has been labeled confidential,
22 but I'm discussing it at a high level.

23 JUDGE KATZ: If it's under the -- if the exhibit is within the
24 proposed protective order, I think we won't be discussing it with an
25 open line. If you want to close the line --

1 MR. RATLIFF: Well, this is very --

2 (Simultaneous speaking)

3 JUDGE KATZ: -- we can --

4 MR. RATLIFF: -- important, Your Honor. If --

5 JUDGE KATZ: Do you want to close the line?

6 MR. RATLIFF: Yeah. Let's do that then.

7 JUDGE KATZ: Okay. One moment please. Can the -- one
8 moment please. Those who should not be here, can exit.

9 MS. BROWN-MARSHALL: And, Your Honor --

10 JUDGE KATZ: Should there be --

11 MS. BROWN-MARSHALL: -- I'd also like to object because
12 this is not rebuttal testimony. The IND was not addressed in anyone's
13 presentation today.

14 JUDGE KATZ: Well, we can take that up after, but first, I'd
15 like to get the record not to -- all right. So one moment. Okay. Is the
16 room as it should be?

17 MS. BROWN-MARSHALL: So the confidential information
18 is JHU's confidential information, so the JHU representatives can stay
19 because it's their own confidential information. It's just the public line
20 that needs to be closed.

21 JUDGE KATZ: Okay.

22 MR. RATLIFF: We don't have any issue with that.

23 JUDGE KATZ: Okay. All right. Okay. Go ahead.

24 MR. RATLIFF: Thank you, Your Honor. And so what we've
25 heard today from JHU are representations that [REDACTED]

1 [REDACTED] with respect to the study that's described in the
2 MSR. And Dr. Oberstein talks about this in his declaration, this is
3 Exhibit 1115, at paragraphs 38 through 44. And he explains that
4 when he looks at that IND, what did JHU do?

5 All the public disclosures we talked about the Lipson
6 publication, for example, and Brommer, and Topalian. That single
7 patient that was an MSI-high colorectal cancer patient, that was part
8 of the rationale for doing the study. The fact that Pembrolizumab was
9 being used to treat cancer patients and showing efficacy, that was part
10 of the rationale. It was nothing about we don't know what's going to
11 happen.

12 And, more importantly, when you look at the IND, Exhibit
13 1116 at 24, [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]

17 Now here's the situation. The irrefutable fact, and it comes
18 down to this because it's important for the analysis. We have to be
19 mindful that JHU's claims, they derive from one clinical study. That's
20 the -- and there's only one clinical study. It's the same clinical study
21 described in detail in the MSR. And it's just a two-step treatment
22 method.

23 It's not the case that JHU, after the MSR was posted, went off
24 and did a study, and then changed the treatment method. And then
25 came up with some new or different method, and then patented it, and

1 that's what we're talking about. No. It's the same study. It's the same
2 treatment method that was disclosed in the MSR. We can't forget that.

3 Now one other point, in particular, when we're looking at the
4 study itself, and we have slide 22 up, the study -- and we walked
5 through this for how the study at each step describes what's
6 happening. And so the person of ordinary skill, when you're looking
7 at the study and you see -- and again, this is a method of soliciting
8 patients -- the patient naturally thinks and the doctor naturally thinks,
9 well, if we're going to be in this arm, arm 1, we need to be tested to be
10 MSI-high. That's how it works.

11 And even Dr. Golberg, and we can bring up our slide 30, this is
12 a JHU declarant, even Dr. Goldberg in his deposition admitted that if
13 you perform the treatment method that's set out in the MSR, you have
14 to get to a point where MSI-high colorectal cancer patients are tested
15 first, or else you'll never fill that arm. He said that. So we think it
16 teaches it for sure that you have to test first, and then you give the
17 drug in response. Now --

18 JUDGE KATZ: Okay. Mr. Ratliff, are we passed talking about
19 the confidential --

20 MR. RATLIFF: We are.

21 JUDGE KATZ: -- part?

22 MR. RATLIFF: We are, Your Honor.

23 JUDGE KATZ: Counsel?

24 MS. BROWN-MARSHALL: Yes, Your Honor.

25 JUDGE KATZ: Okay. All right. Then let's open up the --

1 MR. RATLIFF: Your Honor, may I proceed?

2 JUDGE KATZ: Just a minute. Let me get the line open again.

3 Okay. Go ahead please, counsel.

4 MR. RATLIFF: Thank you, Your Honor. Now, Your Honors,
5 during JHU's presentation involving anticipation and a large part
6 about obviousness, the discussion got very confusing because they
7 were going back and forth whether or not you're treating a group of
8 patients, or a single patient, or multiple patients. But we know the
9 claim language itself only requires treating a patient. This is not about
10 treating a group.

11 This is really about JHU trying to insert this negative limitation
12 into its claims. And one thing in particular that JHU did, and it
13 undercuts its argument, is that it did file a provisional application at
14 the time that there was no data. Why go through the process of filing
15 a provisional application and saying that you have an invention trying
16 to set your mark that you have an invention if you don't think you
17 actually have something? It doesn't make any sense. And that time,
18 when it's filed a provisional application, that was on November 13th,
19 2014, this was more than a year after the MSR had actually published.
20 So they had no data.

21 Now the other thing I want to address is claim construction,
22 because JHU made some claim construction arguments particularly
23 about what the Board did. Can we bring up JHU's Demonstrative
24 Exhibit slide 5?

1 Now I want to bring this up because as we understood it, I don't
2 think JHU has it right as to the Board's claim construction at the
3 institution decision. JHU makes it sound like the Board was looking
4 at the term "in response to," those three words, and then saying that
5 meant after. But as we understood the Board's institution decision,
6 that -- the institution decision claim construction is that the Board
7 wasn't narrowly focused on the words "in response to," but it was
8 looking at the entire context of the arguments.

9 And as we saw, and I walked through it, the Board noted the
10 causal relationship as well as the temporal aspect of the claims. And
11 so looking at that two-step treatment method, there's a causal
12 relationship between the two steps. And the second step occurs after.
13 So that makes complete sense. So we don't think it's a fair
14 characterization of what the Board was actually doing. We think the
15 Board actually really got it right here.

16 Now the experimental use expectation is what that sounds like.
17 It can be an experimental use exception to a use, a public use. But we
18 don't have that here. The MSR is a printed publication. And they
19 admit that they have no law supporting it. And they say, well, people
20 haven't made those arguments yet. Well, I wonder why. It's a well-
21 established precedent that printed prior art does not have an
22 experimental use exception.

23 Now we also want to take a look at some of the quotations that
24 JHU brought up because they're really not fair quotations from the
25 record. So the first one, if we can take a look at JHU slide number 48.

1 On slide 48, they point to Merck's declarant Dr. Neugut, and they say,
2 "You're not relying on Pernot for disclosing the in-response-to claim
3 limitation, right?" And he says, "Correct." Well, the clarity in this
4 question is not there. In this deposition, they were talking a lot about
5 anticipation. For sure, for anticipation, he's not relying upon Pernot.

6 But more importantly, if we look at Dr. Neugut's deposition, a
7 portion that JHU did not cite, what do we see? And this is Exhibit
8 2163 at page 151, line 17 to 152, line 6. And he's asked the question,
9 "You are not relying on Pernot for the testing claim limitation,
10 correct?" And his answer is, "I would say that I'm relying on Pernot
11 for the conduct of the clinical trial, which involves both testing, and
12 then following up the testing with giving Pembrolizumab in response
13 to the results of the testing. I don't think it's limited to testing." So
14 that's a clear example where the declarant is talking about both
15 limitations, testing and giving the drug in response to, and relying on
16 Pernot. It's not the truth from what they quoted on the slide.

17 So let's take a look at JHU slide 57, which is another out so
18 context quote from Dr. Neugut. So here what they ask in the question,
19 "Is there anything in the MSI-high study record that tells a POSA that
20 the protocol will be successful or have a positive outcome?" And he
21 says, "No." Well, they don't show you the testimony right before that,
22 and this is at Exhibit 2163. Let's bring it up. His deposition, page
23 137, lines 8 through 15.

24 And what was he asked? "At the time the MSI-high study
25 record was first posted oncologists could not know the results, right?"

1 His response, "Well, we've discussed this a little bit. They could not
2 know the exact results, but as I said, they can anticipate that there
3 would be -- that the drug would be efficacious." He says it right there.
4 They're choosing what to show Your Honors. And what they're
5 choosing is not showing you the complete picture.

6 And if we also turn to -- we turn to Dr. Neugut's deposition,
7 let's look at Page 115, and lines 20 to 24. This is another portion of
8 his deposition that JHU did not show Your Honors. And he was
9 asked the question, "In your opinion is that based on the MSI-high
10 study record, a POSA would have anticipated seeing positive results
11 from carrying out the MSI-high study record?" His response.
12 "Precisely."

13 Now I want to talk about another portion. So if we take a look
14 at JHU slide number 62. And so here they show this slide to try to
15 make the point that Dr. Oberstein, when he talks about
16 immunotherapy, it doesn't have much context. It could be exercise. It
17 could be anything. But that's just not true.

18 When you look at the actual testimony that's in the record that
19 they haven't showed you, and for example, this is Dr. Oberstein
20 testimony Exhibit 2404 at page 206, lines 8 through 21, what is he
21 doing? He's explaining that context matters. It depends on what
22 you're looking at and how they're using the term immunotherapy. So
23 he says, "I think a person of ordinary skill would have to evaluate
24 each reference in its context.: So JHU is just showing you part of the
25 story.

1 Now JHU also brought up the Pernot reference, and they said,
2 well, when you look at Pernot, and you look at Pernot closely, it does
3 not talk about -- it doesn't talk about the ongoing clinical trials that
4 involve the MSR. And he said Pernot selected what clinical trials
5 they think was positive and what would be fruitful, but it doesn't show
6 these particular ones.

7 Well, when you look at the Pernot article, and this is Exhibit
8 1006, and you look at Pernot's table, this table 1, Pernot makes very
9 clear that the ongoing clinical trials that he's referring to are those that
10 were in the National Cancer Institute Registry. So the MSR, that trial
11 just didn't happen to be in the registry.

12 But what we know as of the alleged invention date of July 10,
13 2015, you had not only the MSR in the public domain for more than
14 two years, but you also had the study that BSM was doing for the
15 same treatment with another PD-1 inhibitor treating patients that had
16 MSI-high colorectal cancer. So it's just really not a clear
17 representation.

18 And JHU also said that for BMS, that the BMS -- for doing the
19 BMS study, that there was only one patient. No one knew what
20 would happen. But let's take, again, a look at the timing with respect
21 to what was known and what was the background at the time of the
22 alleged invention date. You had the MSR disclosing that two-step
23 treatment method, and you also had another clinical study by another
24 company.

1 And when we look at the MSR in particular, you have two
2 sophisticated companies doing this study. So you have two
3 sophisticated organizations. You have JHU, and you also have Merck
4 working together. Nothing about it is an invitation to investigate.
5 Nothing about it is unreal.

6 And then JHU also made a point, and this is what they were
7 saying over and over again, the supposed baseline failure. And we
8 don't have to go over the details, but I just invite Your Honors to take
9 a look again at the submissions that we referred to earlier in the
10 confidential portion.

11 JUDGE KATZ: Okay. Mr. Ratliff, we are at about three and
12 half minutes or so.

13 MR. RATLIFF: Thank you, Your Honor. So I just want to go
14 back to the MSR and look at slide 22 just to make it absolutely clear
15 because this is a case about anticipation. It is a case about disclosure
16 of a two-step treatment method.

17 And if we look at slide 23, what we're showing here on the slide
18 is that first claim step highlighted in yellow, and we see it in the MSR
19 study record. It's that arm 1. It does not matter that they're treating
20 other patients in other arms. The claim doesn't have a negative
21 requirement. It's about disclosure.

22 If we go to slide 26, this is the second step in the method. This
23 is the in response to determining that the patient is MSI-high. We see
24 here in the claim in green the in-response-to limitation. And where
25 does it appear? Right here in the MSR at 4.

1 I mean just think about it. A person of ordinary skill picking up
2 the MSR. Looking at this particular treatment method, looking at a
3 study inviting patients to be treated. You know that you're going to be
4 tested. That you need to be tested for this arm to have positive
5 colorectal cancer.

6 And then because you're being tested, what's the point of the
7 study is to get treatment. And what that treatment is is the
8 therapeutically effective amount of Pembrolizumab. And that's the
9 same amount that's actually in the patent. It's the only amount that's in
10 the patent.

11 And one additional point, Your Honors, this goes to the testing.
12 When you look at the patent itself -- and just make no mistake, when
13 you look at the patent itself, it discloses as part of the methods that
14 you actually have to test -- that it was tested first. So we know that
15 that's happened. It's only logical. And that's in the patent.

16 So we submit when you look at the entire record here, and
17 consider the preponderance of the evidence, the MSR is clear. It is a
18 critical document that only requires disclosure of the treatment
19 method. The inherent results that just comes along with it, that's part
20 of the Federal Circuit law. That's part of the precedent.

21 And so considering the presentations today and what has been
22 discussed, JHU has been vacillating back and forth whether its claims
23 are treating multiple patients, or a patient, or a group of patients, and
24 really trying to assert a negative limitation. And I think they have
25 agreed that inserting a negative limitation to the claim is highly

1 inappropriate. And that is the only way that they're arguing this case.
2 That's the crux of their argument. It is the foundation. So we submit,
3 Your Honor, that all challenged claims here are unpatentable.

4 JUDGE KATZ: Okay. Thank you. Ms. Brown-Marshall, or
5 whoever -- I'm sorry. You're -- okay. And you'll have 10 minutes.
6 Okay.

7 MR. RATLIFF: Your Honors, is it -- I believe there was five
8 minutes reserved.

9 JUDGE KATZ: I think there was 10 minutes from the end of
10 the --

11 MR. RATLIFF: Added on?

12 JUDGE KATZ: Yeah. From -- there was five -- there were
13 five extra minutes.

14 MR. RATLIFF: Okay.

15 JUDGE KATZ: Okay. All right.

16 MS. BROWN-MARSHALL: Thank you, Your Honors. May
17 it please the Board. As an initial matter, I would like to object to the
18 fact that Petitioner's rebuttal included a number of new arguments.
19 All of that deposition testimony that you saw that they put up on the
20 fly that was not included in their slides, that was not included in their
21 briefing, and Patent Owner did not have a chance to either review that
22 testimony, or respond to that testimony here at the hearing because it
23 was all brand new. And that we would ask that the Board, at the very
24 least, provide us with additional post-hearing briefing to deal with
25 those new arguments that were raised during Petitioner's rebuttal.

1 JUDGE KATZ: That's something that we'll take up after.

2 MS. BROWN-MARSHALL: Okay.

3 JUDGE KATZ: And let you know.

4 MS. BROWN-MARSHALL: Thank you, Your Honor. If we
5 could pull up slide 81. So the first argument that I'd like to address is
6 Petitioner's arguments about co-extensiveness. And it was a bit
7 unclear from their presentation about what specific parts of Keytruda
8 were -- so JHU's presentation, let's be clear, that these specific parts of
9 the Keytruda label that we are alleging practiced the claimed -- that
10 JHU's patented claims are specific indications.

11 So when a drug is purchased, it comes with a package insert, or
12 label. And on that label, there are FDA-approved indications. There
13 are two indications on the Keytruda label that are directed specifically
14 to MSI-high colorectal cancer. You can see on the slide that this
15 indication 1.8 and indication 1.9. JHU's not alleging that Keytruda as
16 a drug practice is coextensive with the claims.

17 It's these specific indications which are the directions that are
18 given to a physician will be administering Keytruda, how to
19 administer according to these FDA-approved indications. These two
20 specific indications are coextensive with the claimed methods. It
21 doesn't matter what the other indications are. We're not talking about
22 those other indications. We're talking about these two that are
23 directed specifically to MSI-high colorectal cancer.

24 So, in fact, the Merck product, Keytruda, as represented in these
25 two FDA-approved indications are coextensive with the claimed

1 methods. And this is a slightly different situation. Normally, you're
2 talking about two competing companies that have a widget, and one
3 widget has a new feature. That is not the case here. This is the FDA-
4 approved indications are completely coextensive with the claimed
5 benefits.

6 And I just wanted to add a cite. So we're talking about the
7 dependent claims. Dr. Goldberg, JHU's expert addressed the
8 independent -- or the dependent claims, and how they align with the
9 indications on the label. And that's at paragraphs 75 and 76 of his
10 declaration, which is Exhibit 2090.

11 I also wanted to clarify something from previous questions
12 from Judge Katz, and you were asking about, I believe, the New
13 England Journal of Medicine article, and how that related to
14 reasonable expectation of success. The New England Journal of
15 Medicine article is not prior art. It is the -- it is the inventor's own
16 work. Merck has not alleged that it is prior art, and therefore, it can't
17 be the basis for a reasonable expectation of success because it is not
18 prior art.

19 JUDGE KATZ: Is this exhibit -- which exhibit is this?

20 MS. BROWN-MARSHALL: That would be --

21 JUDGE KATZ: 1056?

22 MS. BROWN-MARSHALL: -- Exhibit 1031.

23 JUDGE KATZ: 1031.

24 MS. BROWN-MARSHALL: Yes.

25 JUDGE KATZ: Okay.

1 MS. BROWN-MARSHALL: Yes. I also want to address the
2 arguments about skepticism. So Merck has alleged that JHU is
3 relying on inappropriate evidence to support the fact that they
4 declined funding until after the preliminary results of the clinical trial
5 were in. There are separate pieces of evidence that will confirm that.

6 So if you look to the patent, at column 3, line 46 through 48, it
7 says -- this is what the JHU inventors told patent office, Merck
8 donated the study drug, reviewed the final drafts of the protocol, and
9 of this manuscript. The clinical study was primarily funded through
10 philanthropic support. And they made that same statement in the New
11 England Journal -- the New England Journal of Medicine Article, too.

12 If you go to Page 2, and on Page 2, it says -- and this is from the
13 New England Journal article, "Merck donated the study drug and
14 reviewed the final drafts of the protocol and of this manuscript before
15 submission. They did not participate in the analysis of the data."

16 And also, if you look at Page 10 of that same New England
17 Journal article, it gives a list of the entities that supported the clinical
18 trial, the first of which is Swim Across America Laboratory at Johns
19 Hopkins University. And it gives another list of several other
20 philanthropic organizations that supported the clinical trial. Merck
21 does not appear on that list.

22 I would also point out that Merck in their rebuttal made certain
23 arguments related to long-felt need and whether a long-felt need
24 existed. Look at what Merck said. Look at Merck's own statements
25 that were made contemporaneously. Those bear -- those are more

1 impactful than anything that it says today, and sort of spinning what
2 happened in the past. Look at the contemporaneous statements.

3 On anticipation, Petitioner's counsel referred to the Schering
4 case, this is the case that requires that for an inherency, that a
5 limitation be necessarily present. The Schering case is distinguishable
6 on the facts from this case. So first, the claim addition of Schering
7 was a compound claim, not a method claim.

8 And that's important because in that case, the prior art disclosed
9 a method that necessarily and inevitably generated the claim
10 metabolite. So you practiced that method in the prior art. You
11 administered that drug, 100 percent of the time in the human body a
12 metabolite is generated. And that's not true here.

13 And also, the court in Schering specifically limited their
14 decision to just that metabolite. And they said that you could draft a
15 patent claim that could avoid anticipation. For instance, you could
16 claim a method of administering the metabolite, or some sort of
17 corresponding pharmaceutical composition. Just because that method
18 produced the metabolite, doesn't mean that anything associated with it
19 is also inherently disclosed.

20 Furthermore, there's nothing inevitable or necessarily present
21 about JHU's results unlike the metabolite in Schering. This doesn't
22 happen 100 percent of the time. As you can see from the results in the
23 colorectal cancer patients, their method doesn't work 100 percent of
24 the time. It worked in a significant number, but not 100 percent of the

1 time. Therefore, it does not meet the bar of being necessarily present
2 under Schering.

3 And, finally, in Schering, there was no question of what the
4 prior art disclosed. They all agree that the method that was in the
5 prior art reference undisputedly disclosed administration of the drug
6 to humans, which necessarily and inevitably formed the claimed
7 metabolite. Here, the MSR doesn't disclose multiple limitations in the
8 claimed method, so therefore, the results are not inherent based on
9 Schering.

10 I'd also like to address counsel's statements about the IND that
11 they mentioned. An IND is an investigational new drug application
12 that was needed to perform the clinical trial. It's not prior art, was not
13 a public statement, a statement to the FDA. And that language that he
14 cited about the hypothesis and some of the other explanations was
15 recited verbatim in the specification of the patent. This was not
16 something that they were trying to hide. They gave those statements
17 to the Patent Office. And that's at -- if you look to the patent at
18 column 2, line 19 through 33.

19 Again, would just like reiterate that JHU's construction is not an
20 unclaimed negative limitation. It is built into the claimed structure. It
21 is built into the claimed term, in the term in response to. And that
22 according to Federal Circuit precedent in the Honda case, that is a
23 proper and appropriate way to interpret the claim. So based on that,
24 Your Honors, I would like to request that the Board confirm
25 patentability of all the challenged claims.

1 JUDGE KATZ: Okay. All right. Thank you very much.
2 Okay. Thank you, everybody, for an interesting argument. Did you --
3 Mr. Ratliff, were you --

4 MR. RATLIFF: Just only one minor thing, Your Honor. We
5 don't believe there's any need for briefing.

6 JUDGE KATZ: Okay.

7 MR. RATLIFF: If Your Honor looks at the record, I think
8 we've only cited to deposition --

9 JUDGE KATZ: Okay.

10 MR. RATLIFF: -- answers that they --

11 JUDGE KATZ: All right. We will let you both know if we
12 require any further briefing. We certainly won't be considering any
13 new arguments that were brought up during the hearing. But we'll let
14 you know if we need any briefing on it.

15 MR. RATLIFF: Understood.

16 JUDGE KATZ: Okay?

17 MS. BROWN-MARSHALL: Thank you, Your Honor.

18 JUDGE KATZ: Thank you so much. All right. Thank you,
19 everybody. And particularly, thank you to our LEAP practitioners
20 who were excellent. Ms. Stauring and Ms. McCormick, thank you so
21 much. We hope to see you again. And with that, if we have anything
22 else from my panel members. Okay. Then we will take the case
23 under advisement and close the record at this point. Thank you.

24 (Whereupon, the proceedings in the above-entitled matter were
25 concluded at 5:24 p.m.)