1

2 UNITED STATES PATENT AND TRADEMARK OFFICE

3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4 HIGHLY CONFIDENTIAL | PROTECTIVE ORDER

5 ----------x

6 MERCK SHARP & DOHME LLC,

7 Petitioner,

8 -against-

9 THE JOHNS HOPKINS UNIVERSITY,

10 Patent Owner.

11 ----------x

12

13 CASE IPR2024-00240
U.S. Patent No. 11,591,393 B2

14

15 STENOGRAPHIC DEPOSITION OF:
PAUL E. OBERSTEIN, M.D.

16 Wednesday, February 19, 2025
7:59 a.m. - 3:21 p.m. | Pages 1 - 320

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22 Reported stenographically by:
Richard Germosen, FAPR, CA CSR No. 14391

23 RDR, CRR, CCR, CRCR, CSR-CA, NYACR, NYRCR
NCRA/NJ/NY/CA Certified Realtime Reporter

24 NCRA Realtime Systems Administrator
Job No. J12413091

25 BILLING FR Ref. 52261-0005IP1

1
2 STENOGRAPHIC DEPOSITION on behalf of Patent Owner
3 of PAUL E. OBERSTEIN, M.D., taken in the above-entitled
4 matter before RICHARD GERMOSEN, Fellow of the Academy of
5 Professional Reporters, Certified Court Reporter,
6 (License No. 30XI00184700), Certified Realtime Court
7 Reporter-NJ, (License No. 30XR00016800), California
8 Certified Shorthand Reporter, (License No. 14391),
9 NCRA/NY/CA Certified Realtime Reporter, NCRA Registered
10 Diplomate Reporter, New York Association Certified
11 Reporter, NCRA Realtime Systems Administrator, taken at
12 the offices of PAUL HASTINGS LLP, MetLife Building, 200
13 Park Avenue, New York, New York 10166, on Wednesday,
14 February 19, 2025, commencing at 7:59 a.m.
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2 A P P E A R A N C E S: (CONT'D.)

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2 I N D E X

3 WITNESS EXAMINATION

4 PAUL E. OBERSTEIN, M.D.

5 BY ATTORNEY BROWN-MARSHALL 8

6

7 E X H I B I T S

EXHIBIT NO.	DESCRIPTION	PAGE
Exhibit 1150	document entitled Rebuttal Declaration of Paul E. Oberstein, M.D.	29
Exhibit 1003	document entitled Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H.	38
Exhibit 2405	document entitled Gastrointestinal Cancer - Gastroesophageal, Pancreatic, and Hepatobilia 4042	165
Exhibit 2406	document headed HHS Public Access	170
Exhibit 1005	document MERCK EX1005	263

1

2 E X H I B I T S (CONT'D.)

3 EXHIBIT NO.	DESCRIPTION	PAGE
4 Exhibit 2061	Merck document JHU2061	291
5		
6 Exhibit 2131	document JHU2131	301
7		
8 Exhibit 2408	document entitled Amendment	303
9	#1	
10		
11 Exhibit 2409	document entitled Amendment	305
12	#2	
13		
14 Exhibit 2410	document entitled Amendment	306
15	#3	

16 **original exhibits returned with original transcript by THE SULLIVAN GROUP OF COURT REPORTERS to
17 FISH & RICHARDSON PC
(exhibit index concluded)
18

19 ***Exhibits 2408, 2409, and 2410 as deemed confidential under the Protective Order.
20

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24

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1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 ----------
3 P R O C E E D I N G S
4 7:59 a.m.
5 ----------
6 CERTIFIED STENOGRAPHER: On the
7 stenographic record 7:59 a.m.
8 Good morning. My name is Rich
9 Germosen. I am a Certified Stenographic
10 Reporter. My license is available for
11 inspection.
12 - - -
13 (Whereupon, the Certified
14 Stenographic Reporter administered the oath to
15 the witness.)
16 - - -
17 P A U L E. O B E R S T E I N, M.D.,
18 (the witness produced a New York State driver's
19 license), having been first duly sworn or affirmed,
20 was examined and testified as follows:
21 EXAMINATION BY ATTORNEY BROWN-MARSHALL:
22 BY ATTORNEY BROWN-MARSHALL:
23 Q. Good morning, Dr. Oberstein.
24 A. Good morning.
25 Q. Would you please state your full

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1 name and address for the record.
2 A. Paul Eliezer Oberstein, 644 West
3 232nd Street, Bronx, New York.
4 Q. And, Dr. Oberstein, have you been
5 deposed before?
6 A. I have been deposed before, yes.
7 Q. Okay. How many times?
8 A. As far as I recall, just one time.
9 Q. Okay. And what sort of matter was
10 that deposition related to?
11 A. As I recall, it related to a
12 medical malpractice case.
13 Q. And were you serving as an expert
14 in that case?
15 A. I was not serving as an expert.
16 Q. Were you a fact witness in that
17 case?
18 A. I was a party in that case.
19 Q. Okay. And you understand that you
20 are here testifying today under oath; correct?
21 A. That's correct.
22 Q. Okay. And that you understand that
23 according to that oath, you are required to
24 tell the truth, the whole truth, and nothing
25

1 but the truth; correct?
2 A. Yes.
3 Q. And will you do that?
4 A. Yes.
5 Q. The court reporter here is taking
6 down everything that I say and that you say,
7 so we need to make sure that we speak loudly
8 and clearly and not speak over each other.
9 Is that understandable?
10 A. Yes.
11 Q. And now, I'm planning to take a
12 break probably about every hour or so, but if
13 you need to take a break before that, just let
14 me know, but the one thing that I ask is that
15 if there is a question pending, please answer
16 the question, and then we can take a break
17 after that, okay?
18 A. Sounds good.
19 Q. Is there any reason why you can't
20 give your best testimony today?
21 A. No.
22 Q. Okay. No medications that might
23 interfere with your ability to give your best
24 testimony?
25

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2 A. No.

3 Q. No car accidents on the way to the

4 deposition?

5 A. No.

6 Q. Okay. Have you previously served

7 as an expert in a legal matter before?

8 A. Yes, I have.

9 Q. Okay. Was that a patent-related

10 matter?

11 A. So I have served in a

12 patent-related matter, yes.

13 Q. Okay. And just generally, what

14 sort of technology was that related to?

15 A. The patent matter was related to a

16 medication, a pharmaceutical drug.

17 Q. Okay. What type of drug?

18 A. Can you clarify the question?

19 Q. Well, you said it was related to a

20 pharmaceutical or a drug. Just generally what

21 type of drug?

22 A. It was a chemotherapy agent.

23 Q. Okay. But you weren't deposed in

24 that matter in which you served as an expert?

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25 A. Correct. I -- I did some

1 preliminary work with the company -- with a
2 law firm, but did not lead to a deposition
3 yet.
4 Q. Okay. So it's an ongoing matter?
5 A. It is an open matter, yes.
6 Q. Okay. And do you anticipate that
7 you will be filing an expert report in that
8 matter?
9 A. So I don't know yet. I've not
10 begun such a report or received an assignment
11 to do that.
12 Q. Okay. And as a part of your work
13 as an expert in that matter, have you been
14 asked to review any patents?
15 A. Yes, I reviewed patents in that
16 matter.
17 Q. Okay. Are you the inventor on any
18 patents?
19 A. Not that I'm aware of.
20 Q. Okay. Have you previously worked
21 on any projects that resulted in patents being
22 issued?
23 A. So I partly answered the previous
24 question vaguely, because I presume so, but
25

I've not been a named patent holder, and I'm not certain whether or not any of the projects I've worked on have led to patents.

Q. Okay. But you're not aware of being an inventor on any patents?

A. Correct.

Q. Are you familiar with the structure of a patent?

ATTORNEY RATLIFF: I object to the form of the question.

A. Yes, I believe so.

Q. Okay. So you're familiar with the patents having a specification section?

A. Yes.

Q. Okay. And you're familiar that patents have claims as part of the patent?

A. Yes.

Q. Are you familiar with the patent examination process?

A. Yes.

Q. Okay. And what is your understanding of a patent examination process?

A. Can you be more specific about that?

2 Q. Well, you said you're familiar with
3 the process. I just want to know sort of at a
4 high level what your understanding is of what
5 that process is.
6 A. So my understanding is that a group
7 of proposed inventors will submit a patent to
8 the Patent Office and the Patent Office will
9 then evaluate that patent and make a
10 determination about patentability. I also
11 understand from reviewing this case that
12 others can then challenge the patent, and
13 there are times where it will come back and be
14 revisited.
15 Q. And what sort of challenges do you
16 understand that can be made to a patent that's
17 already issued?
18 A. So I understand from this case that
19 some challenges to a patent may be issued if
20 the patent is anticipated in the prior art or
21 is obvious from the prior art. I'm sure there
22 are many other reasons why such things can be
23 challenged.
24 - - -
25 (Clarification requested by the

1 stenographer.)

2 - - -

3 A. Why a patent can be challenged, but

4 those are the ones I'm familiar with from this

5 case.

6 Q. And you mentioned anticipation.

7 What is anticipation?

8 A. So as I understand, anticipation is

9 where the claims of the patent are previously

10 reported in a prior work of art that would be

11 publicly available.

12 Q. And you also mentioned obviousness.

13 What is your understanding of obviousness?

14 A. So my understanding of obviousness

15 is that a person of ordinary skill of the art

16 with the prior art references might be able to

17 deduce all of the claims within the patent.

18 Q. And, Dr. Oberstein, you understand

19 that you are testifying today as an expert in

20 an inter partes review proceeding or IPR

21 proceeding; correct?

22 A. Yes, I understand that.

23 Q. Okay. And you understand that IPR

24 proceedings, including deposition transcripts,

2 are public; correct?
3 ATTORNEY RATLIFF: I object to the form
4 of the question, as well as to the premise of
5 the question.
6 A. So I am not aware of that and I
7 don't know if that's true.
8 Q. Okay. And did counsel inform you
9 that the transcript from this deposition will
10 be publicly available on the USPTO website?
11 ATTORNEY RATLIFF: I object to the form
12 of the question.
13 A. That is not something I ever
14 discussed with my counsel.
15 Q. And before we get started,
16 Dr. Oberstein, I notice that you have several
17 piles of documents in front of you. What are
18 those documents?
19 A. So I have several. I have my
20 rebuttal declaration that I submitted in this
21 patent case. I have a copy of the '393
22 patent, the MSI study record, several
23 declarations, including from Dr. Lonberg,
24 Dr. Goldberg, Dr. Le, and Dr. Pardoll, as well

25 as Dr. Neugut, and then several -- actually,

1 six source articles that I reference in my
2 declaration.
3 Q. Okay. And which articles are
4 those?
5 A. So these are articles by Steinert;
6 Champiat; Chapelle; Benson, sorry, there are
7 seven. Hamid, Pernot, and Salipante.
8 Q. And are those clean copies or do
9 those copies have any sorts of annotations on
10 them?
11 A. These copies do not have any
12 annotations.
13 Q. So they're all clean copies?
14 A. Of the articles?
15 Q. Of all of those documents?
16 A. So everything is clean. I have
17 several stickies, Post-its in my rebuttal
18 declaration.
19 Q. And where are those stickies
20 located?
21 A. So I have three. Two of them are
22 next to exhibits in the appendix. One is
23 Exhibit 1135 and one is Exhibit 1137.
24 Q. Why do you have stickies next to
25

1 Exhibit 1135 and 1137?
2 A. So I place notes next to those
3 because in my review of my declaration, I
4 noted that I had not actually reviewed the
5 depositions prior to signing my declaration.
6 I had reviewed the declarations of those
7 names, people, but I confused it and wrote
8 "deposition" by mistake.
9 Q. Okay.
10 A. So I'd like to remove those
11 essentially.
12 Q. Okay. And which depositions are
13 those?
14 A. That was one, 1135 was the
15 deposition of Jennifer Newberger.
16 Q. Okay.
17 A. And Exhibit 1137 was a deposition
18 of Brian Segers.
19 Q. So you did not review the
20 deposition transcripts of Ms. Newberger or
21 Dr. Segers?
22 A. Correct, but I reviewed their
23 declarations, which was my mistake.
24 Q. And I see that you have at least
25

2 one other sticky note in there.
3 A. Yes.
4 Q. What is that one?
5 A. I have one other sticky note, which
6 is in Paragraph 188 of my declaration, where I
7 wrote that my opinion is consistent with
8 Dr. Neugut's declaration and deposition
9 testimony. I had not -- as I recalled, had
10 not reviewed Dr. Neugut's deposition prior to
11 signing this declaration -- my declaration. I
12 have subsequently reviewed it and it was
13 available to me, but I had not reviewed it yet
14 by the time I signed the declaration.
15 Q. Okay.
16 A. My review of that deposition has
17 not changed any of my opinions in this case.
18 Q. Okay. So you'd like to make a
19 correction to Paragraph 188 to remove the
20 mention of Dr. Neugut's deposition; correct?
21 A. Correct.
22 Q. Okay. Are there any other changes
23 that you would like to make to your
24 declaration?

25 A. There are none that I would like to

1 make or none that I'm aware of that need to be
2 made.
3 Q. And, Dr. Oberstein, when were you
4 first engaged to work on this case?
5 A. Can you define "engaged" perhaps?
6 Q. Well, let's start: When were you
7 first contacted with respect to this case?
8 A. So as I recall, I was first
9 contacted in the summer of 2024, this past
10 summer, about potentially consulting in
11 regards to this case.
12 Q. And who contacted you in the summer
13 of 2024?
14 A. So I apologize, I'm very poor with
15 name recollection, but an attorney from the
16 Paul Hastings law firm or perhaps it wasn't an
17 attorney. A representative from the Paul
18 Hastings law firm.
19 Q. And that representative, is that
20 one of the attorneys present here today?
21 A. I do not believe that the initial
22 contact was from one of the people present
23 today.
24 Q. Is it a male or a female attorney?
25

1 A. I don't recall. It was an email.
2 Q. An email.
3 And when did you first speak with
4 someone from the Paul Hastings law firm about
5 this case?
6 A. So shortly after that initial
7 contact, when I expressed an interest in
8 speaking, I had a telephone conference with
9 members of the Paul Hastings law firm.
10 Q. And which members were those?
11 A. I don't recall the names.
12 Q. Are they one of the attorneys that
13 are present here today?
14 A. I believe several of the attorneys
15 here today may have been part of that, but I
16 don't recall exactly.
17 Q. And have you signed a formal
18 engagement letter with respect to your work in
19 this case?
20 A. Had I or have I?
21 Q. Have you?
22 A. I have, yes.
23 Q. Okay. And approximately when did
24 you sign that engagement letter?
25

A. So approximately the summer of 2024. I don't recall if it was -- which month in the summer. Perhaps June or July.

Q. And did you have any other conversations with anyone from the Paul Hastings law firm prior to the signing that engagement letter in June or July of 2024?

A. I do not recall having any other conversations.

Q. Okay. So it was just that one conversation with the members of the Paul Hastings law firm prior to signing the engagement letter?

A. Correct.

Q. Okay. And what did you discuss in that conversation prior to signing your engagement letter?

A. So as I recall now, though this is my recollection, they gave me a very general sense that they were looking for an expert to evaluate in the case, to understand whether I had the time and felt I had the expertise to do that.

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I recall that they discussed with

2 me that there is a patent about a purported
3 method of treatment and that there were prior
4 art documents that discuss some of the factors
5 in the patent, and they wanted to know if I
6 could evaluate those and give an assessment as
7 to whether the claims of the patent were
8 previously revealed in the prior art
9 references or -- or previously taught by the
10 MSI study record.
11 Q. Was Dr. Neugut involved in that
12 conversation?
13 A. No.
14 Q. Are you acquainted with Dr. Neugut?
15 A. What do you mean by "acquainted"?
16 Q. Do you know each other?
17 A. I do know Dr. Neugut. I haven't
18 seen him in quite some time, but I do know of
19 him and do know him.
20 Q. Okay. Have you spoken to
21 Dr. Neugut about any of the matters involved
22 in this case?
23 A. I have not.
24 Q. How many hours have you worked on
25 this case?

2 A. So I don't have an exact number of
3 hours. I estimate somewhere in the range of
4 30 to 50 hours in review of all the documents,
5 declarations, and depositions in preparation
6 of my declaration, but I certainly do plan to
7 sit down and tally it up. I don't have that
8 exact number right now.
9 Q. And that 30 to 50 hours, does
10 that -- is that the number of hours that
11 you've billed for this case?
12 A. So no, that is not.
13 Q. That is not?
14 A. (Indicating.)
15 Q. Okay. How many hours have you
16 billed on this case?
17 A. Again, I don't have an exact
18 number, but I think I billed somewhere between
19 20 to 25 hours so far for the work that I've
20 done, and obviously have more to submit.
21 Q. So 20 to 25 is the number that
22 you've currently submitted bills for. You
23 have outstanding hours that you haven't billed
24 for yet?
25 A. Correct.

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1 Q. And if you add up those currently
2 billed, plus outstanding billed, that would
3 total that 30 to 50 hours of work that you
4 previously estimated --
5 A. That's what I estimated, yes.
6 - - -
7 (Unintelligible, simultaneous
8 testimony interrupted by the certified
9 stenographer.)
10 - - -
11 CERTIFIED STENOGRAPHER: "30 to 50
12 hours" what at the end?
13 Q. 30 to 50 hours of work that you
14 previously estimated?
15 CERTIFIED STENOGRAPHER: That's correct
16 you said?
17 A. Yes, that's my estimate.
18 BY ATTORNEY BROWN-MARSHALL:
19 Q. What is your hourly rate for this
20 case?
21 A. So as I detail I think in my -- as
22 I know in my declaration, my rate is $800 an
23 hour.
24 Q. Do you do any consulting work aside
25

2 from the legal work that you've done on this
3 matter and the other patent matter that you're
4 working on?
5 A. Yes, I do.
6 Q. Okay. And what is your hourly rate
7 for the consulting work that you do?
8 A. So I would say it varies between
9 around 650 to a thousand dollars an hour, but
10 in that range, depending on the nature of the
11 work.
12 Q. So of that 30 to 50 hours,
13 approximately, that you've worked on this
14 case, how much of that was spent preparing
15 your declaration?
16 A. So in essence, everything I did up
17 to the submission of my declaration was part
18 of preparing for my declaration, because I was
19 reviewing all of the important documents from
20 the case, including the declarations of
21 others, the patent, the prior art, and so I
22 would say the majority of that time has been
23 dedicated to preparing background information
24 and then actually compiling my declaration.

25 Q. So if we focus just on the drafting

of the declarations, so putting aside document review and those types of tasks, approximately how many hours have you spent drafting your declaration?

ATTORNEY RATLIFF: I object to the form of the question.

A. So it's hard for me to give a specific answer. I spent several hours, as I said, reviewing documentation starting to draft the declaration, going back to documentation to understand exactly which terminology to use, and then revising the declaration.

So, again, I would say a large part or a majority of that time was spent in preparation and in evaluation or revision of the declaration.

Q. Who wrote the first draft of your declaration?

A. What do you mean by "first draft"?

Q. Well, you put pen to paper for the first time, who was the person that first put words on the paper?

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A. So I believe I put the first words

on the paper. I submitted my initial -- I wrote down my initial thoughts after evaluating the prior art and submitted my conclusions and my thoughts of that as an email to -- maybe it was not an email, maybe it was actually in person, with the trial team -- with the, sorry, legal team, and then we worked on expanding that and drafting it into a full declaration.

Q. Have you prepared or assisted Merck in preparing any other documents in this case other than your declaration?

A. I don't believe so.

Q. Do you anticipate filing any declarations in any related matters to this case?

A. I do not.

Q. And, Dr. Oberstein, you said that you have a copy of your declaration; correct?

A. That's correct.

Q. Okay. So we're looking at Exhibit 1150, the Oberstein declaration.

- - -

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(Whereupon, document entitled

1 Rebuttal Declaration of Paul E. Oberstein,
2 M.D., is received and marked as Exhibit 1150
3 for Identification.)
4 - - -
5 CERTIFIED STENOGRAPHER: Number 1150.
6 BY ATTORNEY BROWN-MARSHALL:
7 Q. Dr. Oberstein, your declaration,
8 Exhibit 1150, includes a list of materials
9 considered; correct?
10 A. Which list are you referring to?
11 Q. So there is a list of materials
12 considered in your declaration; correct?
13 A. I'm sorry, my question was: Which
14 list are you referring to?
15 Q. I'm referring to the list of
16 materials considered.
17 ATTORNEY RATLIFF: I object to the form
18 of the question, as well as to the premise of
19 the question.
20 A. Perhaps you can clarify where in
21 the declaration you're referring to?
22 Q. So if you go to Page 8, just above
23 Paragraph 18, there is a section header
24 called: Materials considered.
25

2 A. Yes, I'm there.
3 Q. Okay. And this is a list of the
4 materials that you considered in formulating
5 your opinions that are contained in this
6 declaration; correct?
7 A. That is correct.
8 Q. And that list also includes the
9 documents that are listed in Appendix A; is
10 that correct?
11 A. That is correct.
12 Q. With the correction that you were
13 removing Exhibits 1135 and 1137; correct?
14 A. That is correct.
15 Q. So the materials that are listed in
16 this materials considered section at
17 Paragraphs 18 and 19, and materials listed in
18 Appendix A, are those all the materials you
19 reviewed in coming to your opinions in this
20 case?
21 A. So the materials listed in the --
22 as you said, in Page 8 or Paragraph 18,
23 Section 4, and the materials in the appendix
24 were the information that I utilized to

25 evaluate the case and to evaluate the '393

2 patent from the perspective of the person of
3 ordinary skill, and enabled me to come to the
4 conclusion that each and every claim
5 limitation in the patent is included in the
6 prior art.
7 They were sufficient for me to make
8 that conclusion. There were other sources
9 that may have come across my awareness during
10 the preparation, but I was able to make that
11 conclusion based on the material I described
12 here.
13 Q. But you didn't list those other
14 resources that came across your awareness;
15 correct?
16 A. So I listed resources that I felt
17 were necessary for me to come to the
18 conclusion that I described in the beginning
19 of my declaration, that each and every claim
20 limitation of the '393 patent is included in
21 the MSI study record and the prior art.
22 Q. What other materials did you
23 consider that you didn't list in your
24 materials considered in your declaration?
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. So I don't have specific examples.

2 As part of my independent research, to come to
3 my conclusions, I looked at many manuscripts,
4 and there were certainly some that I looked at
5 that were not included here, that I think did
6 not add to the strength -- were not necessary
7 for me to make that conclusion.
8 Q. So you're not relying on any of
9 those additional manuscripts to support the
10 opinions in your declaration?
11 A. That is correct.
12 Q. In your work in this case, did you
13 review any memos or depositions or documents
14 related to the case that are not listed in
15 this materials considered section?
16 A. So as I stated -- you mean -- I'm
17 sorry, can you clarify the question?
18 Q. So you previously spoke about
19 references that you reviewed that are not
20 listed in the materials considered section.
21 Did you review any case-related materials that
22 are not listed in the materials considered
23 section?
24 ATTORNEY RATLIFF: I object to the form

25 of the question.

2 A. As I stated earlier, I did review
3 Dr. Neugut's deposition, which is not listed
4 in this list of materials considered. As I
5 stated, it did not change my conclusion in
6 this case about the underlying conclusion of
7 my declaration.
8 Q. Did you review the petition that
9 Merck filed in this case?
10 A. Which petition?
11 Q. So you understand that this is an
12 IPR proceeding which starts with a petition
13 that is filed by the petitioner?
14 A. Yes.
15 Q. Okay. Did you review Merck's
16 petition in this case?
17 A. Do you have that petition for me to
18 refresh my memory?
19 Q. No, I don't. I'm just wondering if
20 you reviewed it?
21 A. I don't recall specifically if I
22 reviewed it or not.
23 Q. Okay. Did you review any of the
24 responses that Johns Hopkins has filed in this
25 case?

2 A. Again, can you tell me how many
3 responses there were or --
4 Q. There is two responses. There is a
5 preliminary response and then there is a
6 patent owner's response. Did you review any,
7 either of those responses?
8 A. So I certainly recall reviewing the
9 patent owner response, POR.
10 Q. Uh-huh.
11 A. I don't recall if I reviewed the
12 other one or if it was available to me.
13 Q. Okay. But you didn't list Johns
14 Hopkins patent owner's response in your list
15 of materials considered?
16 A. That's correct, because as I said,
17 the materials considered, the ones that I
18 thought were essential in me forming my
19 primary conclusion, which is that each and
20 every claim limitation in the '393 patent is
21 included in the prior art, specifically in MSI
22 study record with other prior art, and I did
23 not think that was necessary or changed my
24 conclusion.
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25 Q. In your work in this case, were you

2 shown any other docs other than those listed
3 on your list of materials considered?
4 A. So as I just stated, I definitely
5 recall seeing the patent owner response, as
6 well as some other filings in front of the
7 Patent Office.
8 Q. Okay. What other filings were
9 those?
10 A. I don't recall the exact specifics
11 of any other filings in front of the Patent
12 Office.
13 Q. So aside from filings of the Patent
14 Office, were you shown any other documents,
15 other than those in your materials considered
16 list, in your course of your work in this
17 case?
18 A. And when you say "shown," what do
19 you mean by that?
20 Q. Did Merck or its attorneys provide
21 you with any additional documents?
22 A. I do not recall Merck or its
23 attorneys providing me any documents besides
24 those listed in the materials considered and
25 Appendix A.

Q. And the patent owner's response; correct?

A. Correct.

Q. Dr. Oberstein, as part of your work in this case, you reviewed Dr. Neugut's declaration; correct?

A. That is correct.

Q. And if you'd turn to Appendix A, which is the very last couple of pages of your declaration, this is a list of the exhibits cited by Dr. Neugut in his declaration; correct?

A. You're asking if they're the same exhibits? Where do you want me to turn to?

Q. So if you're at Appendix A?

A. Of my declaration?

Q. Of your declaration?

A. Yes.

Q. These are exhibits -- these are the exhibits that Dr. Neugut relied on in formulating his opinions in his declaration; correct?

ATTORNEY RATLIFF: I object to the form of the question.

2 A. I'm sorry, these are the exhibits
3 that I relied on to prepare my declaration.
4 Q. Let me ask this a different way.
5 What is the source of the documents
6 that are listed in Appendix A?
7 A. I don't understand the question.
8 Q. How did you identify the documents
9 that you reviewed that are listed in Appendix
10 A?
11 A. Again, I -- I looked at the
12 documents that I used in preparation of my
13 declaration.
14 Q. How did you decide to look at those
15 documents?
16 A. Some of them were primary documents
17 that I found. Some were provided to me by
18 counsel. Some were referenced in other
19 people's declarations or depositions.
20 Q. Do you have a copy of Dr. Neugut's
21 declaration?
22 A. I do.
23 Q. Okay. Could you open that up?
24 ATTORNEY BROWN-MARSHALL: So this is
25 Exhibit 1003.

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 - - -
3 (Whereupon, document entitled
4 Declaration of Alfred I. Neugut, M.D., Ph.D.,
5 M.P.H., is received and marked as Exhibit 1003
6 for Identification.)
7 - - -
8 CERTIFIED STENOGRAPHER: Number 1003.
9 BY ATTORNEY BROWN-MARSHALL:
10 Q. Dr. Oberstein, are you familiar
11 with Exhibit 1003?
12 A. I did review Exhibit 1003,
13 Dr. Neugut's declaration.
14 Q. Okay. If you would turn to the
15 back pages starting on Page 90. I'm sorry,
16 yes, Page 90 of 97. And if you would -- so do
17 you see on Page 90 where it says: Appendix A,
18 and then it gives a list of exhibits?
19 A. Yes.
20 Q. Okay. And these are the exhibits
21 that Dr. Neugut relied on in formulating his
22 opinion?
23 A. That is my understanding of
24 Appendix A and Dr. Neugut's declaration.
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25 Q. Okay. If you would quickly compare

1 Appendix A in Dr. Neugut's declaration to
2 Appendix A in your declaration and let me know
3 if they're the same.
4 A. So I'd rather not do that quickly.
5 You want to take the time to go to each one?
6 Q. Well, the exhibits are numbered;
7 correct?
8 A. Correct, there is over 100
9 exhibits.
10 Q. So Dr. Neugut's declaration starts
11 with Exhibit 101, which is the '393 patent;
12 correct?
13 A. That is correct.
14 Q. Okay. And you understand that in
15 an IPR proceeding, that exhibits maintain
16 their exhibit numbers throughout the
17 proceeding?
18 A. Yes.
19 ATTORNEY RATLIFF: Go ahead.
20 Q. Okay. So if Exhibit 1001 in
21 Dr. Neugut's declaration is the same as
22 Exhibit 1001 in your declaration.
23 ATTORNEY RATLIFF: If that's a
24 question, I object to the form of the
25

1 question.
2 A. I'm just trying to clarify. Do you
3 want me to go through one by one and confirm
4 that each exhibit is either the same or not
5 the same between the two declarations?
6 Q. I don't know if it's necessary to
7 go all the way through, but your Appendix A,
8 you rely on Exhibits 1001 through 1148;
9 correct?
10 A. That is correct.
11 Q. Okay. And Dr. Neugut's
12 declaration, he also relies on Exhibits 1001
13 through 1084; is that correct?
14 ATTORNEY RATLIFF: I object to the form
15 of the question.
16 A. That is correct. Those are
17 different numbers you're just saying?
18 Q. So both you and Dr. Neugut rely on
19 Exhibits 1001 through 1084; correct?
20 ATTORNEY RATLIFF: I object to the form
21 of the question, as well as to the premise of
22 the question.
23 A. So I would need some time to go
24 through each exhibit to say whether that's
25

1 true. We both do quote Exhibit 1001 and
2 Exhibit 1084, if that is your question.
3 Q. So your Exhibit A includes the
4 materials that Dr. Neugut relied on in
5 formulating his declaration, the opinions in
6 his declaration; correct?
7 A. So in my declaration, I utilize
8 many of the same materials Dr. Neugut
9 utilized. Again, without going through each
10 exhibit one at a time, I can't clarify -- I
11 can't confirm whether there are any materials
12 in Dr. Neugut's declaration that are not
13 referenced in mine, and I know vice versa
14 there certainly are.
15 Q. Did you review all of the
16 references that Dr. Neugut relied on in
17 formulating his opinions?
18 A. I reviewed the references that
19 Dr. Neugut utilized in forming his opinions,
20 yes.
21 Q. Okay. And you included those on
22 your materials considered?
23 A. As I said before, included
24 information in my materials considered if I
25

1 thought it was helpful and important for me to
2 establish my primary conclusion, which is that
3 each and every claim limitation of the '393
4 patent was included in the MSI study record
5 and available material at the critical date of
6 July 10 of 2015.
7 Q. Dr. Oberstein, I didn't ask you
8 about your conclusions. I asked you about
9 your materials considered.
10 ATTORNEY RATLIFF: If that's a
11 question, I object to the form of the
12 question.
13 A. So my materials considered were the
14 materials I considered in formulating my
15 conclusion, so I included the things that I
16 thought were important to justify and to
17 support my primary conclusion.
18 Q. Are there any materials that
19 Dr. Neugut relied on that you decided not to
20 include in your materials considered list?
21 A. I don't recall any specific
22 examples, but again, I would have to review
23 everything he relied on and the appendix to
24 tell you whether or not there are any specific
25

1 examples.
2 Q. So in your declaration, you note
3 numerous opinions of Dr. Neugut that you agree
4 with; correct?
5 A. There certainly are many things
6 that I agree with Dr. Neugut and quote in my
7 declaration, yes.
8 Q. And I counted those up and there
9 are over 75 instances in your declaration
10 where you note that you agreed with
11 Dr. Neugut; correct?
12 ATTORNEY RATLIFF: I object to the form
13 of the question.
14 A. So you're asking if your count is
15 correct? I did not count them up.
16 Q. Does that sound like a reasonable
17 ballpark?
18 ATTORNEY RATLIFF: I object to the form
19 of the question.
20 A. So I don't have a reasonable
21 ballpark. I could state that I agree with
22 Dr. Neugut on many points and quote him in
23 that context when I agree in my declaration.
24 Q. All right.
25

1 Were there any opinions from
2 Dr. Neugut that you disagreed with?
3 A. So I didn't evaluate Dr. Neugut's
4 declaration with an eye to agreeing or
5 disagreeing with what he stated.
6 My role here as an independent
7 expert was to evaluate the '393 patent, and
8 from a person of ordinary skill at the
9 critical date of July 10, 2015, I evaluated
10 that each and every claim limitation in that
11 patent was previously taught in the prior art,
12 including the MSI study record. That is what
13 I described in my declaration and what I went
14 out to do. I don't have specific rebuttal or
15 comments on Dr. Neugut's declaration.
16 Q. But there is no instances in your
17 mind of issues or opinions that Dr. Neugut
18 provided that you didn't agree with?
19 A. I cannot agree with that statement
20 without giving it more serious thought and
21 going through his declaration with that
22 question in mind. That was not the task I
23 sought after in this expert testimony.
24 Q. So how did you decide which
25

1 opinions of Dr. Neugut's that you agreed with?
2 A. So I evaluated -- I read
3 Dr. Neugut's declaration, carefully evaluated
4 points he raised and sources that he brought,
5 and I included the things that I felt were
6 important for me and important for the
7 conclusion that I came to in this declaration.
8 Q. So you evaluated each of
9 Dr. Neugut's opinions?
10 A. So I evaluated all of the
11 information in light of the goal that I -- the
12 goal that I had, which was to give an
13 independent review of the '393 patent in light
14 of prior art.
15 Q. But you identified over 75
16 instances where you agreed with Dr. Neugut;
17 correct?
18 ATTORNEY RATLIFF: I object to the form
19 of the question.
20 A. I don't have a specific number, but
21 as I said, there are many instances in which I
22 agree with Dr. Neugut, as I stated in the
23 declaration.
24 Q. So you evaluated his opinions. You
25

1 identified many opinions of Dr. Neugut's with
2 which you agreed, but you didn't identify any
3 opinions from Dr. Neugut with which you
4 disagreed?
5 ATTORNEY RATLIFF: I object to the form
6 of the question, as well as to the premise of
7 the question.
8 A. So I did not say that and I do not
9 agree with your statement. I specifically
10 wrote in my declaration the points that I
11 agreed with. I did not make any listing
12 anywhere of things I didn't agree with or
13 compile such a list.
14 Q. I understand that you didn't make a
15 listing of it, but I'm asking: As part of
16 your objective evaluation where you looked at
17 Dr. Neugut's opinions, you identified ones
18 that you agreed with, but you didn't identify
19 any that you disagreed with?
20 ATTORNEY RATLIFF: I object to the form
21 of the question, as well as to the premise of
22 the question.
23 A. So, again, what I laid out here and
24 what I tried to be very clear about was the
25

1 specific objective of evaluating the prior art
2 and the '393 patent, coming to a conclusion of
3 what a person of ordinary skill as of the
4 critical date of July 10, 2015 would have
5 concluded, and my conclusion is that each and
6 every claim limitation in the '393 patent is
7 included in the MSI study record and prior
8 art.
9 That is what I am comfortable
10 describing in my declaration, and that's where
11 I utilized Dr. Neugut for points where I
12 agreed with him about my findings and where he
13 stated it in a similar fashion.
14 Q. So you cherry-picked the opinions
15 of Dr. Neugut that aligned with your opinion?
16 ATTORNEY RATLIFF: I object to the form
17 of the question.
18 A. So, again, I conducted an
19 independent review as an outside expert how a
20 person of ordinary skill in the arts would
21 have evaluated the prior art at the time of
22 July 10, 2015, and where Dr. Neugut's opinion
23 was similar or concurrent with what I
24 concluded, I quoted Dr. Neugut affirmatively.

2 Q. So you didn't bother evaluating
3 Dr. Neugut's declaration for opinions that you
4 disagreed with?
5 ATTORNEY RATLIFF: I object to the form
6 of the question, as well as to the premise of
7 the question.
8 A. So I do not agree with that. I
9 evaluated Dr. Neugut's declaration completely,
10 but in my declaration, I sought out to provide
11 expert testimony about the specific question
12 in front of me.
13 Q. I guess what I'm not understanding
14 is how do you objectively evaluate the
15 opinions of another and only identify opinions
16 that you agree with?
17 ATTORNEY RATLIFF: If that's a
18 question, I object to the form of the question
19 and to the premise of the question.
20 A. So I didn't testify in my
21 declaration about items that I disagreed with
22 in my evaluation with any sort of
23 comprehensiveness. I testified specifically
24 about the role of a person of ordinary skill
25 in evaluating available prior art, including

1 the MSI study record and finding taught in
2 that prior art each and every claim limitation
3 of the '393 patent.
4 Q. I didn't ask about formulating your
5 opinion. I'm asking about your assessment of
6 Dr. Neugut's opinions, and you said that you
7 made an objective assessment, correct, of
8 Dr. Neugut's opinions?
9 ATTORNEY RATLIFF: I object to the form
10 of the question.
11 A. So in my declaration, I do not give
12 an overall objective assessment about
13 Dr. Neugut or anybody else for that matter. I
14 point out areas in which other findings
15 support or build my conclusion that I came to
16 and those are the things I quote.
17 Q. I'm not asking about your
18 declaration. I'm asking about your assessment
19 of Dr. Neugut's preparation, and you said that
20 you made an objective assessment of his
21 opinions; correct?
22 ATTORNEY RATLIFF: I object to the form
23 of the question, as well as to the premise of
24 the question.
25

2 A. So prior to including any item in
3 which I quote agreeing with Dr. Neugut, I made
4 an objective assessment as to whether I agreed
5 with that opinion. It does not say what I
6 think about other things in Dr. Neugut's
7 declaration or anybody else's declaration if I
8 didn't specifically discuss them in my own
9 declaration.
10 Q. But I'm asking: When you made that
11 assessment, did you identify any opinions in
12 Dr. Neugut's declaration of which you
13 disagreed?
14 A. So I don't recall any specific
15 examples, but there were many things in
16 Dr. Neugut's declaration that I did not quote
17 or utilize in my own declaration, and so there
18 may be other things that I disagreed with in
19 that declaration. I do not -- again, as I
20 said, my role here was not to compile those or
21 critically list them, and I did not do that in
22 my declaration.
23 Q. So sitting here today, you cannot
24 identify any opinions in Dr. Neugut's
25 declaration with which you disagree?

2 A. So off the top of my head, I don't
3 have any specific examples, and I did not
4 prepare those for my declaration.
5 Q. So you can't identify them sitting
6 here today?
7 A. I want to be very clear. There may
8 be things there. I can't specifically
9 identify any items right now in which I don't
10 agree with Dr. Neugut in his declaration.
11 Q. So, Dr. Oberstein, one of the other
12 exhibits that you've listed on your materials
13 considered is the declaration of Dr. Nils
14 Lonberg; correct?
15 A. That is correct.
16 Q. And did you review Dr. Lonberg's
17 declaration?
18 A. So I did review Dr. Lonberg's
19 declaration.
20 Q. And in your declaration, you
21 include several opinions from Dr. Lonberg of
22 which you disagree; correct?
23 A. That is correct.
24 Q. And did you review any of the
25 exhibits cited by Dr. Lonberg?

2 A. I did review some of the exhibits
3 cited by Dr. Lonberg, yes.
4 Q. Okay. Which exhibits cited by
5 Dr. Lonberg did you review?
6 A. So I cannot recall exactly examples
7 at this time, but in reviewing Dr. Lonberg's
8 declaration, and there was an exhibit that I
9 wanted to understand what he was bringing from
10 that exhibit, I would have looked up that
11 exhibit and I did that.
12 Q. But you didn't include those on
13 your materials considered list?
14 ATTORNEY RATLIFF: Are you representing
15 that to him or is that a question?
16 Q. Did you include any of the exhibits
17 cited by Dr. Lonberg that you ostensibly
18 reviewed in your materials considered list?
19 A. So I did include in my materials
20 reviewed several references that were also
21 quoted by Dr. Lonberg, for example, the MSI
22 study record or the '393 patent, as well as
23 many of these other references I talked about
24 earlier.

25 Q. Did you include any exhibits cited

by Dr. Lonberg that weren't included in Dr. Neugut's declaration?

ATTORNEY RATLIFF: I object to the form of the question.

A. Again, without going back over every single exhibit in Dr. Neugut's declaration, which is not my declaration, I can't be certain that there are any references that are included from Dr. Lonberg that were not in Dr. Neugut's declaration.

Q. Dr. Oberstein, do you understand the numbering conventions of the exhibits in this case?

ATTORNEY RATLIFF: I object to the form of the question.

A. So it was never explained to me. I can make some conclusions based on what I've seen, but I would rather not speculate.

Q. Well, do you understand that the exhibits submitted by Merck begin with a number beginning with 1, so Exhibits 1001, 1003, etc., are Merck exhibits?

A. So are you telling me that or asking a question?

Q. So is that your understanding? You said you had some understanding of the numbering convention.

A. So it seems that way to me, but it was not described to me by anyone that way, so I can't verify if that's true.

Q. And I'll represent to you that exhibits submitted by Johns Hopkins in this case have exhibit numbers that begin with the Numeral 2, so 2001, 2002.

Do you have any exhibits on your materials considered list that begin with the Numeral 2, so any Johns Hopkins' exhibits listed in your materials considered?

A. I do not.

Q. Okay. As part of your review of Dr. Lonberg's declaration, did you review any exhibits submitted by Johns Hopkins University, which would be the exhibits that start with the Numeral 2?

A. So as I said earlier, yes, I did review some of the exhibits that Dr. Lonberg reviewed in his declaration. I cannot specifically recall if they start with the

1 letter two or the letter one and whether he
2 was quoting things that have previously been
3 referenced.
4 Q. Do you understand that Dr. Lonberg
5 cited exhibits that were not included in the
6 Neugut declaration?
7 ATTORNEY RATLIFF: I object to the form
8 of the question.
9 A. Yes, I understand that.
10 Q. Okay. And did you review any of
11 those exhibits that weren't cited by
12 Dr. Neugut in his declaration?
13 A. So I can't recall specifically, but
14 I believe that I did, because I reviewed, as I
15 said, Dr. Lonberg's exhibits to look at what
16 he was quoting from those exhibits, and many
17 of those may -- well, some of them may not
18 have been included in Dr. Neugut's
19 declaration.
20 Q. How many exhibits cited by
21 Dr. Lonberg did you review?
22 A. I do not specifically recall.
23 Q. But you don't cite any of those
24 exhibits in your declaration?
25

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. I'm sorry, what was the question?

Q. You don't cite any of those exhibits in your declaration?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. So I do not include those in Appendix A or in documents cited.

Q. So you didn't cite them in your declaration?

A. As I said, I did not include those in the list of documents that I relied on to make my declaration.

Q. Do you think it's important in your opinions in which you disagree with Dr. Lonberg to address the evidence that he cited in support of his opinions?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

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A. So as I understood it, my

1 assignment in this case was to be an
2 independent expert, to evaluate the
3 information in the '393 patent in light of the
4 prior art for a person of ordinary skill. I
5 did that unbiased, open-minded evaluation of
6 all the information that was available to me
7 and that I could discover, and my conclusion,
8 which I outline here, is that each and every
9 claim limitation of the '393 patent was
10 included in the MSI study record and other
11 prior art at the critical date of July 10,
12 2015, and would have been taught that way to a
13 person of ordinary skill.
14 That's -- I included everything in
15 my declaration that supported me making that
16 conclusion. I did not include specific
17 critiques outside of my conclusion of other
18 experts in this case.
19 Q. So you did not address the other
20 references that Dr. Lonberg cited in support
21 of his opinions with which you disagree?
22 ATTORNEY RATLIFF: I object to the form
23 of the question.
24 A. So I cited references to support
25

1 the opinion that I took in this declaration
2 and included everything that I thought was
3 important to support and to back up that
4 convention that I came to in this declaration.
5 Q. But you didn't address any of the
6 pieces of evidence that Dr. Lonberg cited as
7 being contrary to those opinions; correct?
8 ATTORNEY RATLIFF: I object to the form
9 of the question, as well as to the premise of
10 the question.
11 A. So, again, I specifically looked at
12 this as an independent and open-minded
13 evaluation of the '393 patent and the prior
14 art. I did not specifically go down other
15 people's points and give a rebuttal or
16 counterargument to those points. I looked at
17 this independently utilizing the prior art,
18 and I did review Dr. Lonberg's arguments in
19 his declaration and came to the conclusions
20 that I outline in this declaration.
21 Q. So you say that you didn't
22 specifically go down other people's points and
23 give a rebuttal or counterargument to those
24 points, but you did express the opinion that
25

1 you disagree with Dr. Lonberg's points;
2 correct?
3 A. So in some parts I noted that I
4 disagreed where it was important and
5 summarized my opinion in the case. I also
6 noted some areas where I did agree with
7 Dr. Lonberg. That's not a comprehensive list
8 of every assessment of every statement of
9 Dr. Lonberg.
10 Q. But for those points where you said
11 that you disagreed, you did not directly
12 address the evidence that Dr. Lonberg relies
13 on in support of his opinions with which you
14 disagree?
15 ATTORNEY RATLIFF: I object to the form
16 of the question, as well as to the premise of
17 the question.
18 A. So I specifically explained why I
19 disagreed with Dr. Lonberg and what the points
20 of evidence were that supported my conclusion
21 that Dr. Lonberg is incorrect in the parts
22 that I disagreed with him. I quoted primary
23 sources, specifically the MSI study record, to
24 support the conclusion that I made that each
25

2 and every claim limitation of the '393 patent
3 was previously taught in the MSI study record
4 in prior art and would have been appreciated
5 by a person of ordinary skill as of the
6 critical date.
7 Q. But in doing so, you did not
8 evaluate any of the counterevidence that
9 Dr. Lonberg cited in support of his opinions?
10 ATTORNEY RATLIFF: I object to the form
11 of the question, as well as to the premise of
12 the question.
13 A. What do you mean by "evaluate"?
14 Q. Well, in your declaration, you
15 don't cite to any of the evidence that
16 Dr. Lonberg cites in support of his
17 declaration; correct?
18 ATTORNEY RATLIFF: I object to the form
19 of the question.
20 A. So in the summary at least and in
21 more detail where I disagree with Dr. Lonberg
22 about specific points, I explain why I
23 disagree and why I take the opinion that I
24 came to in this declaration.

25 Q. And the support for that, for those

1 opinions where you explained why you disagree
2 and why you take the opinion that you came to,
3 those are based on materials that are listed
4 in your materials considered list; correct?
5 A. Correct, and those are similar
6 materials to those that Dr. Lonberg quoted.
7 Q. But they don't include the
8 additional evidence that Dr. Lonberg
9 identified in his declaration; correct?
10 ATTORNEY RATLIFF: I object to the form
11 of the question, as well as to the premise of
12 the question.
13 A. So I don't specifically quote
14 Dr. Lonberg's arguments in every regard.
15 Q. That wasn't my question.
16 In your declaration, you do not
17 address the additional evidence that
18 Dr. Lonberg identified in his declaration;
19 correct?
20 ATTORNEY RATLIFF: I object to the form
21 of the question, as well as to the premise of
22 the question.
23 A. So in my initial description of my
24 overall findings, I only quote the primary
25

2 source, which is the -- the primary source of
3 my findings, which is the MSI study record,
4 which is the same source that Dr. Lonberg
5 utilized in his declaration and disagree with
6 him in that regard.
7 Q. But the additional evidence that
8 Dr. Lonberg cited in support of his opinions,
9 with the exhibits that Johns Hopkins
10 submitted, you don't rely on any of that
11 evidence in support of your opinions in your
12 declaration; correct?
13 ATTORNEY RATLIFF: I object to the form
14 of the question, as well as to the premise of
15 the question.
16 A. So I utilized the information that
17 I think is absolutely essential to make the
18 conclusion that I concluded in this
19 declaration and quote what I think is
20 necessary to come to that conclusion. I
21 didn't quote anything else that I thought was
22 not necessary for that conclusion.
23 Q. So you evaluated the exhibits
24 submitted by Johns Hopkins on which

25 Dr. Lonberg replies and you determined that

2 they were nonessential?

3 ATTORNEY RATLIFF: I object to the form

4 of the question.

5 A. What do you mean by "nonessential"?

6 Q. Well, you just said that "the

7 information that I think is absolutely

8 essential to make the conclusion that I

9 concluded in this declaration." So you

10 determined that some exhibits and evidence

11 were essential and some were nonessential?

12 ATTORNEY RATLIFF: I object to the form

13 of the question, as well as to the premise of

14 the question.

15 A. So I approached this as an

16 independent expert and looked at the prior

17 art, as well as the other information

18 available to me, and my conclusion from

19 reviewing the prior art was that a person of

20 ordinary skill, as of the critical date of

21 July 10, 2015, would have found information

22 and been taught by the prior art that each and

23 every claim limitation of the '393 patent was

24 previously taught, specifically in the MSI

25 study record and supporting documentation as I

1 quote. Those are the references that I then
2 put into my declaration to support that
3 conclusion.
4 Q. So, Dr. Oberstein, what do you mean
5 when you use the term "prior art"?
6 A. So generally, by prior art, I refer
7 to information that was public and published
8 and available to a person of ordinary skill at
9 the time of the critical date of the patent,
10 which in this case I utilized July 10, 2015.
11 Q. And what specific pieces of prior
12 art are you relying on for your opinions
13 contained in your declaration?
14 A. So I have a pretty extensive list
15 of what I'm relying on, which includes the
16 materials considered, but of those, I
17 specifically in my declaration review several,
18 I call, key elements, because I quote them in
19 detail, but there are, of course, more, and
20 those include the MSI study record, as well as
21 the six articles that I previously referenced,
22 which I can give you the names if you'd like.
23 Q. That's all right. We've already
24 been through those.
25

How did you identify those key pieces of prior art that you were just discussing?

A. So for the most part, they were identified for me by the attorneys, and then I independently reviewed them to see if they supported or did not support any conclusions that I was likely -- or that I came to make after my review of all the information.

Q. Uh-huh.

Did you identify any pieces of prior art independent of the ones that were provided by Merck's counsel?

A. Yes, I did.

Q. Which pieces of prior art were those?

A. So one example I would give is Exhibit 1148, which is a public listing on ClinicalTrials.gov of a clinical trial of pembrolizumab in patients with MSI-high colorectal cancer.

Q. Are there any other alleged pieces of prior art that you identified independent of the list that was provided to you by

1 Merck's counsel?
2 ATTORNEY RATLIFF: He didn't say
3 allege. I object to the form of the question.
4 A. I'm sorry, can you repeat the
5 question?
6 Q. So you identified Exhibit 1148 as a
7 reference of what you allege is prior art that
8 you identified independent of the list that
9 Merck's counsel gave you; correct?
10 ATTORNEY RATLIFF: I object to the form
11 of the question.
12 A. That is correct.
13 Q. Okay. Are there any other pieces
14 of alleged prior art that you identified that
15 you relied on in forming your opinions in your
16 declaration, other than Exhibit 1148?
17 A. So as part of my independent
18 evaluation for this matter, I certainly
19 identified other prior art that was not
20 included in the list that Merck had provided
21 for me. I did not, as far as I recall, feel
22 that any of those would need to be included to
23 derive the conclusions that I wanted to
24 present or that came up with to present in
25

2 this declaration.

3 Q. So you didn't identify -- strike

4 that.

5 So you didn't rely on any other

6 additional pieces of alleged prior art that

7 you've identified in formulating your opinions

8 that are contained in your declaration?

9 ATTORNEY RATLIFF: I object to the form

10 of the question.

11 A. So I'm not sure if we're saying the

12 same thing, but I would say that the prior art

13 references that I refer to in my declaration

14 were sufficient to justify the conclusion that

15 I came to, that a person with ordinary skill

16 in the art would have found that all the

17 claims of the '393 patent are taught or

18 suggested in the MSI study record, and the

19 prior art references that I quoted, I did not

20 feel that I needed to add any more references

21 to justify and explain that conclusion.

22 Q. And those were the same conclusions

23 that Dr. Neugut reached; correct?

24 A. So there are many similarities

25 between me and Dr. Neugut. I'm not sure that

we say the exact same thing in every regard.
I don't think we do actually.
Q. Okay. Well, where do you differ
from what Dr. Neugut says?
A. As I said earlier, I don't have
specific examples and did not evaluate whether
what I was saying was the same thing as
Dr. Neugut. I came to my independent
conclusion, and where Dr. Neugut had described
a similar conclusion, I referenced his
conclusion.
Q. So you and Dr. Neugut don't have
the same opinions, but you can't identify any
places where they're different?
ATTORNEY RATLIFF: I object to the form
of the question, as well as to the premise of
the question.
A. Again, my role here was not to
evaluate Dr. Neugut's opinions or to judge
them. It was to formulate an independent
opinion. It may be that we have similar
opinions or the same opinion. I did not
evaluate that. I came to my independent
conclusion, and where Dr. Neugut had said

1 something that was similar to what I wanted to
2 write, I referenced his statement of that.
3 Q. So your independent opinion just
4 happens to rely on the same list of prior art
5 that Dr. Neugut relied upon; correct?
6 A. So my independent opinion came from
7 a review of the prior art. It also reviewed,
8 as I describe here, many declarations and
9 depositions and other pieces of information,
10 and my conclusion from that prior art was that
11 each and every claim limitation of the '393
12 patent was previously taught and would have
13 been appreciated by a person of ordinary skill
14 as of July 10 of 2015.
15 ATTORNEY RATLIFF: And, counsel, we've
16 been going over for an hour, so let's take a
17 break.
18 THE WITNESS: That would be great.
19 ATTORNEY BROWN-MARSHALL: Okay.
20 CERTIFIED STENOGRAPHER: Off the
21 stenographic record at 9:04 a.m.
22 - - -
23 (Whereupon, a short recess was
24 taken.)
25

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 - - -
3 CERTIFIED STENOGRAPHER: Back on the
4 stenographic record at 9:16 a.m.
5 BY ATTORNEY RATLIFF:
6 Q. Dr. Oberstein, did you review the
7 declaration of Dr. Richard Goldberg?
8 A. Yes, I did.
9 Q. And did you review any of the
10 exhibits cited by Dr. Goldberg, and for the
11 record, what are you looking at,
12 Dr. Oberstein?
13 A. Dr. Goldberg's declaration.
14 Q. And that is Exhibit Number -- it
15 should be in the corner?
16 A. 2090. Yes, I did look at some of
17 the references that Dr. Goldberg quoted.
18 Q. Okay. Which ones?
19 A. I don't recall specifically right
20 now. It's quite some time ago when I reviewed
21 this, and as I said, when I saw something that
22 I wanted to clarify, I looked it up.
23 Q. Okay. But you don't list any of
24 those exhibits on your materials considered;
25 correct?

1 ATTORNEY RATLIFF: I object to the form
2 of the question.
3 A. So some of those exhibits are
4 overlapped with what I quoted. I'm sorry, I
5 don't understand the question.
6 Q. Okay. Which of Dr. Goldberg's
7 exhibits are you relying on in formulating the
8 opinions in your declaration?
9 A. So I relied on the exhibits that I
10 referenced in my declaration to formulate the
11 opinion in my declaration. Where Dr. Goldberg
12 quotes the same exhibits, we share those
13 exhibits.
14 Q. Okay. So you're not relying on any
15 new exhibits identified by Dr. Goldberg in his
16 declaration?
17 ATTORNEY RATLIFF: I object to the form
18 of the question.
19 A. So I only included the exhibits
20 that I thought were -- that I relied on to
21 come to my conclusion in my declaration. I
22 didn't include anything else that came from
23 other sources that I did not think were
24 necessary to explain and justify my
25

conclusion.

Q. And, Dr. Oberstein, you reviewed the declaration of Dr. Dung Le; correct?

A. I did, yes.

Q. Okay. Did you review any of the exhibits cited by Dr. Le?

And just for the record, Dr. Oberstein, what are you looking at right now?

A. I'm looking at one of Dr. Le's declarations.

Q. And what's the exhibit number?

A. 20 -- I'm sorry, 1145.

I did not rely on any exhibits quoted by Dr. Le that were not included in the exhibit list that I utilized for my declaration.

Q. So, Dr. Oberstein, you rely on what you describe as the MSI-high study record, Exhibit 1005; correct?

A. Yes, I reference that extensively in my declaration.

Q. When was the first time that you read that exhibit?

2 A. That exhibit was something that I
3 reviewed in the summary after Merck reached
4 out to me about representation in this case.
5 I don't recall if I saw that exhibit prior, in
6 the course of my regular research in clinical
7 activities.
8 Q. And you also rely on the Pernot
9 exhibits, Exhibit 1006; correct?
10 A. That is correct.
11 Q. Okay. When was the first time that
12 you saw the Pernot exhibit?
13 A. Again, I know that I was made aware
14 of that exhibit after I engaged with Merck
15 about performing an evaluation for this case.
16 I don't recall if 10 years ago or 15 years ago
17 I saw that exhibit as well.
18 Q. So you have no recollection of
19 encountering the Pernot exhibit prior to your
20 work on this case?
21 A. I have no specific recollection. I
22 look at many articles over the course of time
23 and it was over a decade ago, so I can't say I
24 specifically recall it, but there is a chance

25 I did see it, I just don't specifically recall

that.

Q. And then you also rely on what you called the Chapelle article; correct? Exhibit 1007?

A. That is correct.

Q. And the author's name is actually de la Chapelle; correct?

A. That is correct.

Q. And he's a professor at Ohio State University?

A. He was a professor at Ohio State. I don't know what he's currently doing.

Q. Okay. And you went to medical school at Ohio State; correct?

A. That is correct.

Q. Did you ever encounter Professor de la Chapelle while you were there?

A. What do you mean by "encounter"?

Q. Did you take a class from him?

A. So it was a few years ago. I don't recall taking a class with him, but I do recall hearing him lecture and hearing about some of the work done in his lab.

Q. And when was that lecture?

A. So I recall in the summer of 2003, I think.

Q. And that was while you were a medical student at Ohio State?

A. I'm sorry, let me get my dates right. I apologize. Yeah, in the summer of 2003 is what I recall.

Q. Okay. And was that during your time as a medical student at Ohio State University?

A. Yes.

Q. Okay. So other than attending that lecture by Dr. de la Chapelle, did you have any other contact with him while you were at Ohio State?

A. My recollection of over 20 years ago is that at some point, I reached out and had an email communication with Dr. de la Chapelle about doing research in his laboratory. I did not do research at his laboratory, so as I recall, he either didn't respond to me or there was no available opportunity.

Q. Okay. So other than that email

1 outreach and attending the lecture by
2 Dr. de la Chapelle, did you have any other
3 contact with him while you were at Ohio State?
4 A. Not that I recall.
5 Q. You also rely on the Steinert
6 exhibit, which is Exhibit 1008?
7 A. That is correct.
8 Q. When was the first time that you
9 read the Steinert exhibit?
10 A. So as I recall, the first time I
11 read that was the summer after I was engaged
12 to evaluate this case.
13 Q. And you also rely on the Salipante
14 exhibit, which is Exhibit 1009 -- oh, no,
15 sorry. Correct that. You also rely on the
16 Salipante exhibit, which is Exhibit 1010;
17 correct?
18 A. I have to confirm the numbers.
19 That is correct.
20 Q. When was the first time you read
21 the Salipante exhibit?
22 A. Again, I don't recall specifically
23 having read it prior to engaging in this
24 review in the summer of 2024.

Q. And you also rely on the Hamid exhibit, which is Exhibit 1011; correct?

A. That is correct.

Q. Okay. And when was the first time that you read the Hamid exhibit?

A. So I have recollection of reading the Hamid exhibit when it came out in 2013, but I certainly reviewed it again this summer in 2024 after being engaged to provide expert testimony in this case.

Q. Did you review each of the references listed in your materials considered in Paragraphs 18 and 19 and in Appendix A?

A. I'm sorry, can you say that again?

Q. Did you review each of the references listed in your materials considered in Paragraphs 18 and 19 and in Exhibit A?

A. Yes, I did.

Q. Okay. Did you read each one cover to cover?

A. So I don't think I read everything in Appendix A cover to cover. I think the ones that I quoted here specifically, I did read, as you say, cover to cover, meaning

2 thoroughly. There are some others that
3 were -- potentially I looked at the critical
4 elements that were quoted by other people in
5 the case to verify that it was there and that
6 it was the right context, but I can't say that
7 I reviewed them in detail or can recall all
8 the specific details.
9 Q. And in addition to the references
10 listed in your materials considered, you also
11 looked at some of the references cited by
12 Dr. Lonberg and Dr. Goldberg; correct?
13 A. That is correct.
14 Q. Okay. How many hours did you spend
15 reviewing references that are -- strike that.
16 How many hours did you spend
17 reviewing references in total for this case?
18 A. So I can't recall a specific number
19 of hours. I think pertinent to your earlier
20 questions about how many hours I spent in
21 review, as I review all of this, I think
22 the -- I have to tally up all the hours. I
23 spent quite a considerable amount of time in
24 reviewing records.
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25 Q. But it's not more than 30 to 50

2 hours; correct?

3 A. So I -- I -- I think I have to

4 clarify and go through and count up the exact

5 time. I can't give you an exact number of

6 time based on the fact that I haven't tallied

7 that up yet.

8 Q. But it was your testimony that your

9 total hours spent on this case is 30 to --

10 approximately 30 to 50 hours; correct?

11 A. Correct.

12 Q. Okay. So the number of hours that

13 you spent reviewing can't be more than the

14 total number of hours; correct?

15 A. Correct. So that was an

16 approximate number, and I think that as I go

17 up and tally my numbers, it certainly may

18 change.

19 Q. Do you know how many pages are

20 included in all the references you've listed

21 in your materials considered?

22 A. I do not know how many pages.

23 Q. So we added it up and it's over

24 7600 pages of references.

25 ATTORNEY RATLIFF: If that's a

1 question, I object to the form of the
2 question.
3 Q. So you reviewed over 7600 pages of
4 references in less than 30 to 50 hours;
5 correct?
6 ATTORNEY RATLIFF: So now it sounded
7 like a representation. So I object to that
8 representation, and I'll object to the form of
9 the question.
10 A. So I would not say that. I think
11 that I did keep -- did review all the
12 information that I said I reviewed or I
13 described as reviewing, and I have to count up
14 the hours, and it may turn out that it was
15 more than I anticipated of 30 to 50 hours.
16 Q. But that 30 to 50 hours, even if
17 it's more, also includes the time that you
18 spent working on drafting your declaration;
19 correct?
20 A. That is correct. As I said,
21 reviewing these records had a critical role in
22 my mindset in drafting my declaration.
23 Q. And even though they played a
24 critical role, you still spent less than 30 to
25

50 hours reviewing 7600 pages -- over 7600 pages worth of references?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. So as I said, I didn't keep an exact -- I don't have in my mind an exact tally of the amount of time I spent, and it's very possible that I spent more than 30 to 50 hours when I add it all up, including the review of the records and the preparation of my declaration.

Q. Did you perform a literature search in conjunction with your work in this case?

A. What do you mean by a "literature search."

Q. Did you search for additional references other than the ones provided for you by Merck's attorneys?

A. Yes, I did.

Q. Okay. And how did you go about performing that literature search?

A. So generally, a few different ways.

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One is by utilizing a site called PubMed,

where we have a collection of many or most available public published articles and putting in keywords, such as microsatellite unstable, colon cancer --

- - -

(Clarification requested by the stenographer.)

- - -

A. Microsatellite unstable, colon cancer, immunotherapy, other keywords that would help identify articles.

Another part is by going down the reference list of articles that I identified to look at what they're referring to to see look -- critically here it was the timing of when articles were published to know what might be included in the record that was available to a person of ordinary skill as of July 10, 2015.

I also look at other professional references that we use, such as a site called UpToDate, which is essentially an online encyclopedia of medical knowledge.

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Q. And which of your materials

2 considered were identified by that literature
3 search that you performed?
4 A. So I essentially found additional
5 references that I thought were relevant, but
6 none of them were necessary, in addition to
7 what I described here, to justify and come to
8 the conclusion that I came to that the prior
9 art as of July 10, 2015 described each and
10 every claim limitation in the '393 patent,
11 including specifically the MSI study record
12 and other prior art.
13 Q. So you don't rely on any additional
14 articles you identified via a literature
15 search in formulating your opinions in your
16 declaration?
17 A. I rely just on the articles that
18 were laid out here in materials considered.
19 Q. And none of those were articles
20 that you identified via a literature search?
21 A. I gave you one example prior of
22 something in Appendix A that I identified
23 through a search of a clinical trial record,
24 but outside of that, these were not ones that

25 I independently identified through a

1 literature search.
2 Q. And, Dr. Oberstein, you're not
3 relying on any regulatory filings from Merck
4 with the FDA in formulating your opinions in
5 your declaration; correct?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. What do you mean by "regulatory
9 filings"?
10 Q. So you understand that
11 pharmaceutical companies need approval from
12 FDA to sell a product; correct?
13 A. Pharmaceutical companies?
14 Q. Yes.
15 A. That is correct.
16 Q. Okay. And you understand that
17 Merck has approval from FDA to sell Keytruda;
18 correct?
19 A. That is correct.
20 Q. Okay. Did you review any
21 regulatory -- sorry. Strike that.
22 Did you review any regulatory
23 filings from Merck associated with FDA
24 approval for Keytruda?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I make reference a few times to a package insert of Keytruda. Is that something you would consider a regulatory filing?

Q. So, yes, that could be.

So other than the package insert, did you review any regulatory filings from Merck associated with FDA approval for Keytruda?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I do not recall looking at any that were in addition to the package insert that I described in my Appendix A.

Q. Okay. So other than the package insert, you don't rely on any regulatory filings from Merck associated with FDA approval for Keytruda; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I don't believe I have any of those listed in my materials considered.

Q. Okay. And so you didn't rely on them?

A. If they're not listed in the materials considered, I didn't rely on them.

Q. Okay. Have you had any conversations with any other experts engaged by Merck in this case?

A. Yes, I had two phone conversations with an expert, Dr. Sheridan I believe.

Q. Okay.

A. And I'm very poor at names, so I apologize, but I think I got it.

Q. Okay. So when did that first conversation with Mr. Sheridan occur?

ATTORNEY RATLIFF: Dr. Sheridan.

ATTORNEY BROWN-MARSHALL: Oh, it's Dr. Sheridan.

Q. Apologies. Dr. Sheridan.

A. I don't recall the exact date, but it was, I think, in early January or late December, so in the last couple of months.

Q. Okay. And who participated in that conversation?

A. So it was a Zoom or video

1 conference, so there were several other people
2 on the line. I know some of them I recognize
3 from this team at Paul Hastings. I can't give
4 you every name. Dr. Sheridan, and I don't
5 know if there were other people from
6 Dr. Sheridan's team on the call.
7 Q. And what was discussed on that
8 first conversation with Dr. Sheridan?
9 A. So as I recall, Dr. Sheridan asked
10 me for background information about the
11 diagnosis, staging, and treatment of colon
12 cancer, as well as the way MSI-high colon
13 cancer might be diagnosed and the treatment
14 that you would utilize in that setting,
15 including immunotherapy, such as
16 pembrolizumab.
17 Q. Anything else discussed on that
18 first call?
19 A. So we had a lengthy conversation.
20 I don't recall every single detail. I have
21 some recollection that we discussed some of
22 the percentages of different staging, meaning
23 what percentage of patients have Stage 1,
24 Stage 2, and things of that nature, which is
25

1 relevant, of course, for the treatment
2 described.
3 I also -- I had a second
4 conversation with Dr. Sheridan where I know it
5 was right before I submitted my declaration
6 and reviewed with him some of the conclusions
7 that I had made in my declaration. I don't
8 know if I gave him any of that preliminary
9 information in the first call.
10 Q. So you said that the first call was
11 lengthy. Approximately how long did it last?
12 A. I'd say 30 to 40 minutes.
13 Q. And you said the second
14 conversation with Dr. Sheridan occurred -- was
15 it the day that you signed your declaration?
16 A. It was certainly not the day I
17 signed it, but it was, I think, that week.
18 Q. Okay.
19 A. So I submitted my declaration on a
20 Friday. It was some day earlier in that week,
21 if I recall correctly.
22 Q. Okay. And who attended that second
23 conversation with Dr. Sheridan?
24 A. So a very similar cast of
25

1 characters, attorneys that I know from Paul
2 Hastings, and again, I don't know if there
3 were attorneys from Merck on that call, and
4 Dr. Sheridan, of course.
5 Q. And what was discussed on that
6 second conversation?
7 A. So Dr. Sheridan had some follow-up
8 questions for me, which I recall had more to
9 do with the specific utilization of
10 immunotherapy, such as pembrolizumab or
11 nivolumab for MSI-high colon cancer patients,
12 and I reviewed with him some of my
13 understanding if -- the MSI study record and
14 how in my opinion to a person of ordinary
15 skill in the art an MSI study record
16 anticipated and taught each and every claim of
17 the '393 patent.
18 Q. Did you and Dr. Sheridan discuss
19 anything else on that second call?
20 A. It's very possible. I don't recall
21 every single detail that we discussed.
22 Q. Approximately how long did that
23 second call with Dr. Sheridan last?
24 A. As I recall, it was also around 30
25

1 minutes. Slightly shorter maybe.
2 Q. And have you spoken with Dr. Neugut
3 in conjunction with this case?
4 A. I have not.
5 Q. Do you have an understanding of why
6 you were asked to put in a declaration
7 responding to Johns Hopkins' patent owner
8 response instead of Dr. Neugut?
9 A. I do not.
10 Q. Have you had any conversations with
11 Ross Pierce in conjunction with this case?
12 A. What is Ross Pierce?
13 Q. He was a potential expert
14 identified by Merck.
15 ATTORNEY RATLIFF: I object to the form
16 of the question.
17 A. I don't think so.
18 Q. The name doesn't ring a bell?
19 A. No.
20 Q. Okay.
21 A. But I already said names are not
22 the best, but I do not recall that name or a
23 conversation with anyone outside of this
24 counsel about this case.
25

2 Q. And did you have a conversation
3 with John Bone in conjunction with this case?
4 A. John who?
5 Q. Bone, B-O-N-E.
6 A. I don't think so.
7 Q. So other than Dr. Sheridan, have
8 you spoken with anyone else in conjunction
9 with this case?
10 A. I do not recall speaking to anyone
11 outside of the legal team from Merck and Paul
12 Hastings, who are here, and their colleagues.
13 Q. What did you do to prepare for this
14 deposition today?
15 A. I got a good night's sleep. I read
16 over my declaration and skimmed, as you
17 pointed out by the many pages, some of the
18 other pieces of prior reference and sources
19 that I quote in my declaration.
20 Q. Did you meet with counsel?
21 A. And I met with counsel and reviewed
22 some of that.
23 Q. How many times did you meet with
24 counsel?

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25 A. Overall or specifically in this

1 context?
2 Q. In preparation for the deposition
3 today?
4 A. I think we met four times.
5 Q. Four times? Okay.
6 When was that first meeting with
7 counsel?
8 A. Friday of this past week I believe.
9 Q. Okay. And approximately how long
10 did that meeting last?
11 A. Approximately two hours.
12 Q. Okay. And who was in attendance at
13 that meeting?
14 A. So that was a Zoom as well. So the
15 attorneys from Paul Hastings here were present
16 there and I think that was it.
17 Q. And when did the second meeting
18 with counsel in preparation for this
19 deposition occur?
20 A. The second meeting was this past
21 Sunday.
22 Q. Okay. And --
23 A. Do you need the date or no? I
24 don't remember the date, but what's today?
25

Q. Today is the 19th.

A. So perhaps the 16th, if that's correct.

Q. Okay. And how long did you meet on Sunday the 16th?

A. For roughly three to four hours.

Q. And who was in attendance at that meeting?

A. Again, the same group from Paul Hastings, and I think representatives from Merck might have been on the line.

Q. Okay. And was that also via Zoom?

A. That was done in person.

Q. That was done in person, okay, and when did the third meeting occur?

A. Monday.

Q. Okay. How long did you meet on Monday?

A. Also around four or five hours.

Q. Okay. And who was in attendance at that meeting?

A. The same, the same crew, Paul Hastings and Merck attorneys.

Q. And the fourth meeting?

A. The fourth meeting was yesterday, Tuesday.

Q. Okay. And how long did that meeting last?

A. Around two hours.

Q. And who was in attendance at that meeting?

A. Again, the same group from Paul Hastings and Merck attorneys.

Q. And was that in person or on Zoom?

A. That was also in person.

Q. Did you meet with or speak with anybody other than counsel to prepare for your deposition today?

A. No, I did not.

Q. Dr. Oberstein, you have a medical degree from Ohio State University; correct?

A. That is correct.

Q. And you graduated in 2006?

A. That is correct.

Q. Okay. And then after that, you did a residency in internal medicine at Temple University Hospital; correct?

A. That is correct.

Q. What years were you at Temple University?

A. 2006 to 2009.

Q. And then after that, you did a fellowship in hematology and oncology at Columbia, New York; correct?

A. That's correct. There is a break in between that. Do you want me to add that information?

Q. Sure.

When was the break?

A. So from 2009 to 2010, as well as prior and after, I worked as a hospitalist. So I was an internal medicine certified doctor, and I worked in a hospital essentially moonlighting, meaning covering shifts to provide internal medicine care.

Q. But you weren't providing oncology care when you were moonlighting as an internist; correct?

A. I wasn't providing independent care.

Q. And you were working under the supervision of another doctor?

A. No. I was -- I was providing care independently for internal medicine issues.

Q. Okay. And what sorts of internal medicine issues were you treating when you were working as a hospitalist?

A. Heart attacks, infections, people who couldn't breathe, pneumonia, things like that.

Q. Okay. So after your break when you were working as an internist, then after that you did the fellowship?

A. That's correct.

Q. In oncology at Columbia; correct?

A. That's correct.

Q. Okay. Which years were that?

A. 2010 to 2013.

Q. And do you have any training in immunology?

A. So what do you mean by "training"?

Q. Let's start at medical school, did you receive any instruction or training on immunology?

A. Yes. So immunology is a basic course taught in medical school.

2 Q. Okay. So you had the basic course
3 of immunology in medical school.
4 After medical school, did you
5 receive any instruction or training in
6 immunology?
7 ATTORNEY RATLIFF: I object to the form
8 of the question, as well as to the premise of
9 the question.
10 A. So, yes, during my fellowship, I
11 did a subsequent fellowship in clinical trial
12 design and patient-oriented research. I took
13 graduate-level classes in immunology at
14 Columbia.
15 Q. At Columbia.
16 Do you have any training in cancer
17 genomics?
18 A. I have basic training in cancer
19 genomics as part of medical school and my
20 fellowship training, but I don't have any
21 advanced training in cancer genomics.
22 Q. What did the training in immunology
23 that you received during your fellowship
24 entail?
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25 A. Graduate-level classes and subject

2 matters about immunology, specifically
3 immunology of cancer.
4 Q. And you're currently employed as
5 the service chief in the GI oncology practice
6 with the Perlmutter Cancer Center at
7 NYU Langone Health; correct?
8 A. That is correct.
9 Q. Did you audition for their Super
10 Bowl commercial?
11 A. On the record, I did not.
12 Q. Okay.
13 A. But I was featured in a separate
14 commercial that we're hoping will run soon,
15 where they got a lot of pushback, so I don't
16 know what's going to happen.
17 Q. Okay. We'll have to keep an eye
18 out.
19 A. So watch out for me.
20 Q. Okay. How long have you been
21 employed by NYU Langone Health?
22 A. Seven years. I think March 1 is my
23 anniversary, so it will be seven years on
24 March 1.
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25 Q. And which years? What years does

1 that span?
2 A. March 1, 2018 to today.
3 Q. And you are currently a practicing
4 medical oncologist focused on GI cancers,
5 especially colorectal, pancreatic, and gastric
6 cancers; correct?
7 A. That's correct.
8 Q. When did you first begin treating
9 cancer patients?
10 A. So in, I would say, July of 2010 is
11 when I started treating cancer patients.
12 Q. And that was when you began your
13 fellowship in oncology?
14 A. That's correct.
15 Q. And when did you start focusing on
16 GI cancer patients?
17 A. So actually, I would say within six
18 months of that time. Most fellowships,
19 including the one I did, consist of a small --
20 not a small, but a period of time of clinical
21 knowledge and expertise and research time, and
22 so my research time, which I started within
23 six months of starting fellowship, was focused
24 on GI cancers, and that's where it became my
25

2 focus.

3 Q. And do you treat your GI cancer

4 patients with immune checkpoint inhibitors?

5 A. When it's appropriate, absolutely.

6 Q. And which immune checkpoint

7 inhibitors do you prescribe to your patients?

8 A. So I currently prescribe several

9 FDA approved immune checkpoint inhibitors, and

10 I also engage in clinical trials where we use

11 many checkpoint inhibitors that are not FDA

12 approved or not yet FDA approved.

13 Q. Okay. So let's put aside the

14 clinical trials for a minute, and just talking

15 about the FDA approved immune checkpoint

16 inhibitors that you prescribe.

17 Which specific ones do you

18 prescribe to your GI cancer patients?

19 A. You'd like a list?

20 Q. Sure.

21 A. Nivolumab and ipilimumab;

22 pembrolizumab; dostarlimab. Those are

23 medication, I don't remember the current name,

24 but tremelimumab. There is a drug that I

25 think used to be called MD4736 that now has

2 been approved and has a brand name. I don't
3 recall the brand name, but those are the ones
4 that I recall off the top of my head. There
5 probably are more.
6 Q. And do you prescribe the same
7 immune checkpoint inhibitors to, let's say, a
8 gastric cancer patient as you would prescribe
9 to a pancreatic cancer patient?
10 A. So sometimes we do and sometimes we
11 don't. It depends on why we're giving the
12 immune checkpoint inhibitors, what the
13 indication is, what features of that person
14 are, and what the FDA approval is.
15 Q. So when you prescribe an immune
16 checkpoint inhibitor to one of your GI cancer
17 patients, you prescribe those under an
18 indication that is listed on the label of the
19 drug; correct?
20 ATTORNEY RATLIFF: I object to the form
21 of the question.
22 A. So not necessarily. We often do,
23 but there are times we use medications,
24 quote/unquote, off-label.

25 Q. And when would you use an immune

2 checkpoint inhibitor off-label with one of
3 your GI cancer patients?
4 A. So there may be an instance where
5 one is concerned that an approved
6 immunotherapy has side effects that are
7 intolerable and that another immunotherapy
8 might be more tolerable, and we would use that
9 instead or based on insurance issues,
10 sometimes where an insurance company will
11 approve one and not the other. There could be
12 other factors as well.
13 Let's say treating patients, you
14 know, is quite dependent on the individual
15 patient and the individual circumstances.
16 Q. When did you first start
17 prescribing immune checkpoint inhibitors for
18 your GI cancer patients?
19 A. So I don't have an exact
20 recollection of when I first prescribed the
21 medication. I can't say more than that.
22 Q. Do you remember was it during your
23 fellowship?
24 A. I don't recall -- I recall
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25 utilizing immune checkpoint medications on

clinical trials during that time period, but I don't recall the exact date.

Q. Okay. What clinical trials related to utilizing immune checkpoint inhibitors did you participate in during your fellowship?

A. So I don't recall all the exact specifics right now, but as I mentioned earlier, we were certainly doing an immune therapy study of what's called maintenance immunotherapy with a drug made by a company called MedImmune that I was engaged in and was an investigator in and treated patients with in around that time period of 2013 to 2014.

Q. Okay.

A. I wish I can give you more specifics, but I can't.

Q. Okay. Were you involved in any clinical trials related to pembrolizumab?

A. Ever?

Q. So let's start off with during your fellowship, were you involved with any clinical trials related to pembrolizumab?

A. I don't believe so.

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Q. And prior to 2015, were you

1 involved in any clinical trials related to
2 pembrolizumab?
3 A. So I don't recall exactly when, but
4 I know that as soon as pembrolizumab obtained
5 its first approval in melanoma, its use became
6 quite widespread in clinical trials, and I was
7 definitely involved in clinical trials at that
8 point. I don't have the specific dates for
9 when they started. I think -- I know it was
10 around that time period since the approval
11 came prior to 2015.
12 Q. And do you remember which types of
13 cancer were involved in those pembrolizumab
14 clinical trials that you participated in?
15 A. So I don't recall exactly. I only
16 treat GI cancer, so it was certainly one of
17 those, but I can't recall the exact studies I
18 was involved in at that time period.
19 Q. Okay. Were you -- prior to 2015,
20 were you involved in any clinical trials
21 related to treating MSI-high cancer with
22 pembrolizumab?
23 A. I don't specifically recall if any
24 of the trials I was involved in had specific

2 cohorts for MSI-high patients.
3 I certainly treated colon cancer
4 patients in clinical trials, and they would
5 have been included if the trial wrote it that
6 way, but I don't have a specific recollection.
7 Q. And when you say that you treated
8 colon cancer patients in clinical trials, do
9 you remember which drug was involved in those
10 clinical trials?
11 A. So, again, I don't have the final
12 dates I would say in my head. I know I was
13 involved in a colon cancer trial that would
14 have been a drug called Celecoxib around that
15 time period, and the question was whether that
16 has utilization for colon cancer patients, but
17 I don't recall their specifics.
18 Q. Prior to 2015, were you involved in
19 any clinical trials relating to the use of
20 pembrolizumab in colon cancer patients?
21 A. So as I said before, I don't
22 recall. It's possible, but I can't recall
23 specifics.
24 Q. Have you been involved with any

25 clinical trials related to the use of

2 pembrolizumab in treating colorectal cancer
3 patients since 2015?
4 A. I don't recall specifically.
5 Q. Okay. But you have been involved
6 in clinical trials involving the use of
7 pembrolizumab to treat GI cancers; correct?
8 A. Absolutely.
9 Q. Okay. Which GI cancers?
10 A. So I could speak to the trials that
11 I wrote, which I'll try to remember well, but
12 I -- in 2016, I started a clinical trial,
13 wrote and designed a clinical trial utilizing
14 pembrolizumab for the treatment of gastric
15 cancer, stomach cancer.
16 I've also written studies in
17 pancreatic cancer, and I've certainly -- with
18 pembrolizumab and been involved in other
19 studies with pembrolizumab both in stomach
20 cancer, liver cancer, and something called
21 cholangiocarcinoma or bile duct cancer.
22 Q. And when you say that you wrote a
23 clinical trial, what do you mean by that?
24 A. I mean, that I collaborated with

25 the team to -- I serve as a principal

1 investigator and thus collaborated with the
2 team to design, write, and submit a clinical
3 trial for approval.
4 Q. What's involved in writing a
5 clinical trial?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. That is a very broad question.
9 Q. Okay. Just at a high level.
10 ATTORNEY RATLIFF: I object to the form
11 of the question.
12 A. So, again, it is a very complicated
13 question. Clinical trials have many specific
14 requirements so that they would be understood
15 and describe the rationale, the risks, the
16 inclusion criteria, the analysis. And so
17 writing the clinical trial involves being
18 responsible for the teams that collaborate
19 with all the different parts of putting
20 together a clinical trial.
21 Q. And you mentioned that as a
22 principal investigator, you were involved with
23 submitting a clinical trial for approval.
24 What's involved with submitting a clinical
25

2 trial for approval?
3 ATTORNEY RATLIFF: I object to the form
4 of the question.
5 A. So I was specifically referring to
6 getting it approved at one institution so that
7 one can enroll patients, and at a minimum,
8 that involves, at a minimum, submitting the
9 study and some rationale for the study to a
10 scientific review committee, as well as an
11 institutional review board, or IRB, to obtain
12 approval for that study.
13 In most institutions, like the ones
14 I've practiced in, there are many other layers
15 of requirement to understand how the funding
16 and the resources, the feasibility, patient
17 population, there is a lot of variables that
18 go into those decisions.
19 Q. And have you been involved in
20 dealing with those other variables in the
21 clinical trials that you have participated in?
22 A. So, yes, so certainly in my role
23 currently I'm the director of the GI disease
24 management group at NYU, DMG. And what that

25 role essentially means is that if any

2 investigator within GI cancers has a protocol,
3 it has to go through our committee to
4 determine whether all of those steps are going
5 to be met adequately.
6 Q. Do you prescribe Keytruda to the
7 colorectal cancer patients that you treat?
8 A. To some of them when appropriate.
9 Q. And how do you determine when it's
10 appropriate to prescribe Keytruda to a
11 colorectal cancer patient?
12 ATTORNEY RATLIFF: I object to the form
13 of the question. Expert opinion.
14 A. So, again, that is a very broad and
15 long discussion. I can only reiterate that,
16 you know, almost everything we do is based on
17 teams and collective knowledge.
18 So generally, either we're relying
19 on what's printed, so we go to clinical
20 trial -- I'm sorry, to NCCN or compendia
21 guidelines, which are expert opinion, or like
22 at NYU, we have what are called tumor boards,
23 where we discuss complicated patients, and the
24 discussion will involve literature that's

25 known, the experience of different

1 investigators, the health of the patient, and
2 make a determination whether this is a
3 medication that would be likely to benefit and
4 it's indicated for that patient.
5 Q. Do you routinely test your
6 colorectal cancer patients for MSI-high?
7 A. Yes, our institution tests every
8 single colorectal cancer patient for MSI-high.
9 Q. Okay. And if a colorectal cancer
10 patient -- if their MSI-high test comes back
11 positive, what happens?
12 ATTORNEY RATLIFF: I object to the form
13 of the question.
14 A. Can you clarify what you mean by
15 "what happens"?
16 Q. Uh-huh.
17 Do you use the results of that
18 MSI-high testing that you perform on
19 colorectal cancer patients in making treatment
20 decisions for the patient?
21 A. So one of the reasons that we test
22 for MSI-high and have done this for many, many
23 years is that MSI-high could be a marker for
24 genetic syndrome that predisposes someone and

2 potentially their family to develop colon
3 cancer and other cancers.
4 So one aspect of MSI-high testing
5 is referral to a genetics counselor to
6 understand whether that's a fundamental or
7 germline mutation, and that is something that
8 we certainly do.
9 That may have significant impacts
10 on that person's screening for other cancers,
11 as well as the treatment of their cancer, and
12 potentially family who may have the same genes
13 as they have.
14 Q. And when you're talking about
15 germline mutations, you're talking about Lynch
16 syndrome; correct?
17 A. Correct. The name for a germline
18 mutation in an MMR protein is Lynch syndrome.
19 Q. Okay. If you have a colorectal
20 cancer patient who is MSI-high, would that
21 affect your decision whether or not to
22 prescribe that patient Keytruda?
23 ATTORNEY RATLIFF: I object to the form
24 of the question.

25 A. So, again, it's quite complicated

and it depends on the stage of the cancer of the patient and the other potential treatment options for that person.

Q. Uh-huh.

A. Perhaps you can specify.

Q. So how does MSI-high -- strike that.

How is the stage of the colorectal cancer patient influence the use of MSI-high in making treatment decisions with a patient?

A. So colon cancer very broadly is staged as either being metastatic, meaning incurable for -- by surgery or curable by surgery -- potentially curable by surgery, which is called Stage 1 to 3 colon cancer, and that's the vast majority of colon cancers.

Currently, if a patient has Stage 1 to 3 colon cancer, there is no role for immunotherapy in treatment, as the treatment is surgery, sometimes followed by chemotherapy. We are doing clinical trials to advance that, but that's the current standard of care.

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The role of immunotherapy is

1 currently only relevant in the metastatic
2 patients.
3 Q. And what is the definition of
4 metastatic?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. So generally metastatic is used to
8 describe one of two things, either a cancer
9 that, as I said, is not curable by removing
10 it, so it can't be removed through surgery or
11 some other means, and thus, it's,
12 quote/unquote, incurable by surgery, or a
13 cancer that has spread from its original site
14 of origin.
15 Q. How does metastatic cancer that is
16 incurable by surgery differ from cancer that's
17 unreceptible?
18 A. So if you're using the terminology
19 in that sentence, metastatic cancer that's
20 incurable by surgery means that the metastatic
21 cancer has spread from where it started and
22 there is evidence that cancer cells have gone
23 somewhere else from the site of origin.
24 Q. Can you have metastatic cancer that
25

1 has not spread from where it started?
2 ATTORNEY RATLIFF: I object to the form
3 of the question.
4 A. So as I said earlier, it depends on
5 what context one is using the terminology
6 "metastatic." If you use it in the context of
7 metastatic cancer that is not surgically
8 removable, it would imply two separate things.
9 It has spread and it's not surgically
10 removable.
11 If one just calls the cancer
12 incurable or metastatic, it may refer to a
13 cancer that is in its local spot, but has
14 spread to such an extent to the local tissue
15 that is incurable and unremovable by surgery.
16 Q. So how does that metastatic cancer
17 that has spread to such an extent in the local
18 tissue that's incurable differ from locally
19 advanced cancer?
20 A. So --
21 ATTORNEY RATLIFF: I object to the form
22 of the question, as well as to the premise of
23 the question.
24 A. Yeah, so there are not really
25

2 standard definitions for many of these
3 materials, so, for example, locally advanced
4 cancer is really not an accepted terminology
5 that can transfer from one physician to
6 another physician, meaning one surgeon may
7 look at something and say, This can never come
8 out. It's locally advanced, and another
9 surgeon can look at it and say, I have no
10 problem doing surgery here.
11 So there isn't anything biological
12 that we can use to define locally advanced,
13 and generally, we leave it up to the person
14 who is evaluating the patient.
15 Q. So in your opinion, there is no
16 standard definition of locally advanced
17 cancer?
18 A. I can't speak for all cancers, but
19 for GI cancers, that is generally accurate.
20 There is no standard definition.
21 Q. In your practice, do you prescribe
22 Keytruda to colorectal cancer patients who are
23 MSI-high?
24 A. Sometimes I do, yes.
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25 Q. And in your practice, do you

2 prescribe Keytruda to colorectal cancer
3 patients who are not MSI-high?
4 A. So I generally do not, outside of a
5 clinical trial or some very rare exceptions.
6 Q. As part of your practice, do you
7 regularly read the medical literature?
8 A. So the medical literature is a very
9 broad term. Certainly spent a considerable
10 amount of time reading medical literature. I
11 hardly make a dent in what's out there by
12 doing that.
13 Q. So what is your process for
14 identifying the most relevant medical
15 literature to review?
16 ATTORNEY RATLIFF: I object to the form
17 of the question.
18 A. So I have a few processes. One is
19 I get a daily listing from some cultivated
20 service that tells me what they think is
21 important in the literature, and I do my own
22 independent reading, and I receive journals in
23 my home that I look at, usually online
24 actually nowadays, but I also work within a

25 group and we have regular meetings, and it's

2 sort of an opportunity for people who have
3 found something that they think is relevant,
4 to share it with the group and discuss what it
5 might mean. So we attend things called
6 journal club and other educational meetings,
7 as well as larger meetings with key opinion
8 leaders and Congress meetings.
9 Q. You mentioned that you look at
10 journals online. Which journals do you read
11 online?
12 A. So I would say it's an evolving
13 cast. I currently look at Nature, Journal of
14 Clinical Oncology. Often the New England
15 Journal of Medicine and a journal called
16 Science. In addition, I receive other
17 journals, and I, again, look at many things,
18 depending on whether the headline that is
19 relevant to me and catches my interest.
20 Q. And why did you pick those journals
21 to review?
22 A. The primary reason is that if one
23 serves as a reviewer for a journal, they
24 usually get a complementary subscription to
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25 that journal, and then they just start sending

1 that to you.
2 Sometimes they stop after a year
3 and sometimes they never stop. So these are
4 all journals that at some point, I probably
5 engaged with them, and they started sending
6 things to me, and they're of interest.
7 Q. And would you say that those
8 journals are highly respected journals?
9 A. In general, yes. I don't agree
10 with everything I read, but yes.
11 Q. So you don't agree with everything
12 you read even in highly respected journals?
13 A. Correct.
14 Q. Okay. Are you aware of any
15 research in the field of oncology that was
16 later retracted or corrected?
17 ATTORNEY RATLIFF: I object to the form
18 of the question.
19 A. What do you mean by "the field of
20 oncology"?
21 Q. So you review journals as part of
22 your medical practice; correct?
23 A. (No response.)
24 Q. And I'm assuming that those are
25

2 journal articles that are relevant to your
3 oncology practice; correct?
4 A. That is correct.
5 Q. Okay. So of those journal articles
6 that you review that are relevant to your
7 oncology practice, do you remember any that
8 have been either corrected or retracted?
9 ATTORNEY RATLIFF: I object to the form
10 of the question.
11 A. So it's very common to have
12 corrections, which are usually editorial
13 corrections, of the name or the spelling in a
14 journal. It's exceedingly rare for a journal
15 printed in a high impact publication to be
16 retracted.
17 And I could think of very few
18 examples of that, and say it's much more
19 likely that a journal describing very
20 preliminary scientific work, that is almost
21 speculative, would be retracted, but in the
22 publications that I mentioned, I think it's
23 exceedingly rare for an article to be
24 retracted, and I can't recall a specific
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25 example in GI cancer that comes to mind.

2 Q. Okay. And sometimes when journal
3 articles are published, the journal will also
4 publish letters or comments on those articles;
5 correct?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. So that is correct, but it's highly
9 variable based on the journal as to what
10 format those take and how much review or peer
11 review those undergo.
12 Q. And sometimes those letters or
13 comments can come from authors who disagree
14 with the journal article; correct?
15 A. So again, it depends on the
16 journal. Some journals will not publish such
17 an article or letter and some will.
18 Q. Which journals will publish those
19 type of letters or comments?
20 A. So I don't think journals release
21 their official editorial stance, and I think a
22 lot of it depends on the editorial decision
23 making of the editors of that journal.
24 Q. Uh-huh.
25 A. The New England Journal of Medicine

1 does occasionally publish critical letters.
2 They almost never critique the primary finding
3 of the study and they almost always discuss
4 the implication of that study and what the
5 author said versus what the arguer or
6 discusser thinks.
7 Q. So there can be a disagreement in
8 sort of the medical community about what the
9 implications of a given reference are;
10 correct?
11 ATTORNEY RATLIFF: I object to the form
12 of the question.
13 A. Again, that's incredibly broad
14 statement. It depends on the article and what
15 it's arguing and whether there is room for a
16 different interpretation of those facts or a
17 disagreement with the facts.
18 Q. But that happens sometimes; right?
19 ATTORNEY RATLIFF: I object to the form
20 of the question.
21 A. I would say in clinical trials, in
22 clinical trial research, it's exceedingly rare
23 that someone would challenge the fundamental
24 facts of an article.

Q. What about medical literature that's not related to clinical trials, is it more common to see those challenges to the interpretation of a nonclinical trial medical reference?

ATTORNEY RATLIFF: I object to the form of the question.

A. Yeah, I can't speak very definitively to that. Again, it would probably depend on how clearly defined the outcomes of the study are.

Q. Uh-huh.

A. In clinical trial research, as we see in the MSI study record, it's almost always the case that the authors or the people who conduct the clinical trial will define population involved, the endpoint they're looking at, the treatment they're giving before they start.

Q. Uh-huh.

A. And as long as they report that accurately in the manuscript, it's difficult to argue with those facts or to find challenge with them.

2 Q. Uh-huh.

3 A. Most reviewers, including myself,

4 will always look at a document that's

5 submitted for a clinical trial publication and

6 make sure that it matches what was reported in

7 the clinical trial record at the initiation of

8 the study, and it always does.

9 Q. And you previously testified that

10 some medical literature will contain

11 speculative statements; correct?

12 ATTORNEY RATLIFF: I object to the form

13 of the question, as well as to the premise of

14 the question.

15 A. So I can't speak for all medical

16 literature. I think specifically the journals

17 that I mentioned earlier, again, speaking that

18 there are editors of these journals who make

19 these decisions, but they almost always were

20 not encouraged or would prohibit a speculative

21 statement.

22 In a journal you'd have to support

23 what you're saying with the facts of what you

24 have in the article. There are many, many

25 other journals that are published that may

1 have different standards.
2 Q. And as a reader of a given article
3 or reference, would you approach a speculative
4 statement more critically than you would sort
5 of a factual statement about the results of a
6 trial or something like that?
7 ATTORNEY RATLIFF: I object to the form
8 of the question.
9 A. So I think those statements would
10 be stated very differently, right. If someone
11 said a definitive conclusion, that would be
12 taken in a different light than if they said a
13 speculative statement.
14 Q. Uh-huh.
15 A. I think both would be taken
16 seriously if you take seriously the author of
17 the study.
18 Q. Uh-huh.
19 A. But they have different
20 implications.
21 Q. And what are those different
22 implications?
23 A. One is speculation and one is
24 definitive.
25

1 Q. Uh-huh.
2 And as a reader of an article,
3 would you be more critical or maybe have, you
4 know, read more closely that speculative
5 statement than you would that factual
6 statement?
7 ATTORNEY RATLIFF: Which article, which
8 speculative statement are you talking about?
9 Q. So --
10 A. Yes, can you clarify -- sorry, I'll
11 repeat that.
12 Q. Okay.
13 A. But this is getting very abstract
14 and vague. I mean, I think in general, a
15 person would read an article and have the same
16 level of belief in that article based on the
17 authors and the journal regardless of what the
18 statement is, but again, if you have a
19 specific example, I perhaps can comment on it.
20 ATTORNEY RATLIFF: Counsel, we've been
21 going about an hour. While you're searching
22 for a question, let's take a break.
23 ATTORNEY BROWN-MARSHALL: We'll take a
24 break.

1 THE WITNESS: A break.
2 CERTIFIED STENOGRAPHER: Off the
3 stenographic record at 10:16 a.m.
4 - - -
5 (Whereupon, a short recess was
6 taken.)
7 - - -
8 CERTIFIED STENOGRAPHER: Back on the
9 stenographic record at 10:29 a.m.
10 BY ATTORNEY BROWN-MARSHALL:
11 Q. Dr. Oberstein, as part of your
12 medical practice, do you monitor postings on
13 ClinicalTrials.gov
14 A. So what do you mean by "monitor"?
15 Q. Do you read postings on
16 ClinicalTrials.gov
17 A. So, yes, I frequently do.
18 Q. Okay. And are those postings, are
19 those related to clinical trials that you are
20 participating in?
21 A. So I review a very large number of
22 postings to be honest, I engage in many
23 clinical trials, but, you know, one of the
24 primary uses of ClinicalTrials.gov to me and
25

2 others like me, I think is as we referenced
3 here in Benson I believe, one of the
4 recommended treatments for any metastatic
5 colorectal cancer patient beyond second line
6 therapy is clinical trials, and so very often
7 we'll have a patient in which we know that we
8 should consider clinical trials, and since I
9 don't have offhand knowledge of every single
10 clinical trial, I'll often go to
11 ClinicalTrials.gov, put in their disease and
12 their stage and things like that and look for
13 trials. Patients will often do the same thing
14 and come to me and give me a trial number and
15 ask me what I think about a trial.
16 Q. So other than identifying potential
17 trials for patients, are there any other
18 reasons why you'd check postings on
19 ClinicalTrials.gov
20 A. Yeah, so I think, for example,
21 someone will call me up and say, We have this
22 new compound we're interested in testing in
23 new clinical trials.
24 The first thing you would do is

25 look at ClinicalTrials.gov to see if it's

2 already being tested and what context and
3 learn information from that as well. It's
4 very often one of the primary public sources
5 of information about ongoing clinical trials
6 for a particular drug.
7 Q. And do you limit your review of
8 postings to ClinicalTrials.gov to specific
9 diseases?
10 ATTORNEY RATLIFF: I object to the form
11 of the question.
12 A. So I'm not sure what you mean by
13 that. I treat specific diseases and do
14 research on specific diseases, and that's what
15 I'm primarily interested in. However, there
16 are many, many medications that are being
17 tested in a different setting that would have
18 relevance to the disease that I treat or the
19 setting in which I want to use it in.
20 Q. And when you read a submission on
21 ClinicalTrials.gov related to a clinical
22 trial, do you read that submission with the
23 assumption that that trial will be successful?
24 A. So that's an incredibly vague

25 question and it really depends on the trial,

1 what I know about it, you know, the
2 information, the setting, the sponsor, you
3 know, I incorporate all of the information
4 there to make that decision.
5 Q. So you read those submissions with
6 an eye towards sort of evaluating how
7 successful you think the trial might be based
8 on those factors that you just described?
9 A. So I don't think that was an
10 exhaustive list of factors, meaning, I think
11 it's hard to give a single answer for every
12 single posting on ClinicalTrials.gov about the
13 desire to participate in that trial and what
14 we mean by the likelihood of success or
15 ability for a certain patient to go on that
16 trial.
17 Q. But you sort of review a clinical
18 trial that you might be considering for a
19 patient with a critical eye in that you need
20 to evaluate what you think is the sort of the
21 value of that trial?
22 ATTORNEY RATLIFF: I object to the form
23 of the question, as well as to the premise of
24 the question.
25

2 A. So I'm not sure what you mean by "a
3 critical eye." I think we certainly want to
4 be good stewards and give the right treatment
5 to the right person.
6 Q. And part of that being a good
7 steward is evaluating what you think the
8 potential success of a clinical trial would be
9 before you enroll a patient in that trial?
10 A. So I would certainly want to make
11 sure that it's worthwhile for a patient to go
12 on a trial before recommending the trial to
13 that patient.
14 Q. And you noted in your declaration
15 that: My focus on multidisciplinary
16 collaboration has led to rapid access
17 referrals of patients in our clinics and
18 increased clinical trial participation by over
19 100 percent; is that correct?
20 A. That is correct.
21 Q. Okay. Why is it important to
22 increase clinical trial participation by over
23 100 percent?
24 A. I'm trying to find it. So there
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25 are many reasons likely for trials are

1 valuable. One of the reasons, as I just
2 mentioned, is that for many patients, clinical
3 trials are part of what we consider the
4 standard of care, and thus ideally, every
5 patient with colon cancer who has treated with
6 two prior regimens, excuse me, would have a
7 clinical trial that they can participate in,
8 if appropriate.
9 So the reality is that clinical
10 trials open and close and are for different
11 cohorts and they're very specific, so by
12 increasing both awareness of clinical trials,
13 increasing the range of clinical trials, we're
14 able to give more options to patients.
15 Q. And are clinical trials the method
16 by which new methods of treatment are
17 identified?
18 ATTORNEY RATLIFF: I object to the form
19 of the question.
20 A. So I'm sorry, what do you mean by
21 "methods of treatment"?
22 Q. So one of the purposes of a
23 clinical trial could be to evaluate a new use
24 for a known drug; correct?
25

1 ATTORNEY RATLIFF: I object to the form
2 of the question.
3 A. That is correct.
4 Q. And -- so increasing participation
5 in clinical trials would help support the
6 evaluation of new uses for known drugs;
7 correct?
8 ATTORNEY RATLIFF: I object to the form
9 of the question.
10 A. So not necessarily. There are many
11 clinical trials that don't lead to new uses of
12 drugs, but potentially.
13 Q. What are the other potential
14 benefits of expanded participation in clinical
15 trials?
16 A. So, again, the primary benefit for
17 a patient is to have access to more options
18 for therapy to treat their cancer, help them
19 have a better outcome.
20 Q. So going beyond an individual
21 patient, are there benefits to sort of
22 patients writ large to increasing
23 participation in clinical trials?
24 ATTORNEY RATLIFF: I object to the form
25

2 of the question.
3 A. So I'm not sure what you mean by
4 "patients writ large." Not the person who's
5 on the trial? Somebody else?
6 Q. Are there benefits to, let's say,
7 colorectal cancer patients as a collective to
8 increasing participation in clinical trials?
9 ATTORNEY RATLIFF: I object to the form
10 of the question.
11 A. So I wouldn't say clinical trials
12 per se. It really depends on the quality of
13 the clinical trials.
14 Q. Uh-huh.
15 A. You know, if they're clinical
16 trials that are of quality that they're likely
17 to give new understanding of how to treat a
18 patient, then certainly that could have
19 relevance for, as you put it, the community at
20 large, the community at writ large I guess,
21 but that's why we evaluate clinical trials and
22 we decide, you know, whether this is an
23 appropriate -- or not appropriate, whether
24 this is a clinical trial that is likely to
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25 benefit our patients and it is something that

2 fits within our sphere of treatment.
3 Q. And, Dr. Oberstein, you have a
4 master's in biostatistics from Columbia;
5 correct?
6 A. That's correct.
7 Q. Why did you obtain that degree?
8 A. Why did I obtain?
9 Q. Uh-huh.
10 A. So that degree was done in a
11 federally funded grant program, meaning I
12 submitted a grant, an application was awarded,
13 and they paid for my degree, to support me as
14 what was called a patient oriented research
15 fellowship. And the goal I think of that
16 underlying federal grant is to increase the
17 number of physicians and researchers who are
18 applying the techniques of research for
19 patient-specific cares.
20 My aspect of that was clinical
21 trial design and clinical trial conduct, and
22 so one of the really important parts of
23 clinical trials is the statistics part of it,
24 to make sure that we are asking questions that

25 we can answer in the context of a clinical

2 trial, and that at the end of a successful
3 trial, will have an answer to that question.
4 Q. And that statistical training,
5 that's not something that you learn as part of
6 your medical training; correct?
7 A. So it's absolutely essential to
8 have some basic statistical knowledge as part
9 of medical training and more specifically in
10 oncology, which is a very trial heavy field.
11 We do a lot of clinical trials. As you see,
12 that's one of the standard of cares for a
13 patient. This was well above that. So I did
14 more advanced techniques in statistics in
15 dedicated courses in biostatistics.
16 Q. And how have you used that sort of
17 advanced statistical knowledge in your medical
18 practice?
19 A. So I use it frequently when I both
20 evaluate clinical trials, when I talk to our
21 biostatisticians about designing prospective
22 studies, but primarily in educating our
23 fellows and our junior faculty about how they
24 could use statistics to look at the
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25 literature, look at the data that's printed

2 and understand what exactly it's telling us
3 and how to utilize it in their practice.
4 Q. And as part of your practice, you
5 are involved in designing and conducting
6 clinical trials; correct?
7 A. That is correct.
8 Q. And those clinical trials that you
9 have designed and conducted involve using
10 novel agents, including immunotherapies, for
11 the treatment of colorectal, pancreatic, and
12 other GI cancer patients; correct?
13 A. That is correct.
14 Q. How many clinical trials have you
15 designed?
16 A. So it's a little bit difficult to
17 give an exact answer to that question, because
18 as I think I mentioned a few times, clinical
19 trials really require a very large team of
20 participants for many, many different aspects
21 of the trial, and so there are some that I was
22 the principal investigator and the primary,
23 quote/unquote, designer.
24 Q. Uh-huh.

25 A. But there are many, many, many

1 studies in which I have a role as one of the
2 consultants or one of the key opinion leaders
3 in helping provide direction and design for
4 that trial. So including the more broad
5 definition, I would say probably 30 or 40
6 clinical trials, but it's hard to give an
7 exact number.
8 Of the trials that I've primarily
9 designed and conducted on my own, it's
10 probably in the 5 to 10 number.
11 Q. And were you the principal
12 investigator on those 5 to 10 trials?
13 A. Generally.
14 Q. And what does it mean to be a
15 principal investigator on a clinical trial?
16 A. So, again, a principal investigator
17 can mean many different things and these
18 terminologies are all quite varied depending
19 on the context, so perhaps you can give me
20 some more perhaps to what you mean.
21 Q. Well, you used the term "principal
22 investigator." I'm just trying to figure out
23 what you mean by it when you use it?
24 ATTORNEY RATLIFF: If that's a
25

2 question, I object to the form of the
3 question.
4 A. So let me do perhaps the most
5 common use is that each site, each institution
6 or site, has to have one person who is
7 responsible for overseeing all aspects of the
8 trial and is accountable, and that person is
9 called the principal investigator.
10 Q. Uh-huh.
11 A. In general, that person may or may
12 not have been the one who designed the trial,
13 but at that site for which they serve as
14 principal investigator, they ultimately have
15 responsibility of all of the people involved
16 in the regulatory, the clinical conduct, the
17 reporting, and other aspects of the clinical
18 trial, and need to be familiar with that.
19 Q. Do clinical trials usually have a
20 sort of primary principal investigator?
21 A. So I would say there is really no
22 usual with clinical trials. Some do and some
23 don't. There is really as many flavors as you
24 can imagine.

25 Q. When you make a submission to

1 ClinicalTrials.gov, do you need to identify
2 the principal investigator on your submission?
3 ATTORNEY RATLIFF: I object to the form
4 of the question.
5 A. So in general, in
6 ClinicalTrials.gov, you identify -- I think
7 the term is a study official, which is usually
8 someone in which the, I guess, the HHS or NIH
9 can contact that person for information.
10 That's not always the principal investigator,
11 though sometimes it is.
12 So just, for example, by mistake
13 someone recently posted a clinical trial that
14 included my cell phone number as the principal
15 contact. My phone was ringing off the hook
16 until we corrected that. So that could
17 happen. I was not the principal investigator
18 and that was inappropriate, but very often
19 they will include a contact, but not always.
20 So it always has to include a
21 contact for the FDA to reach out to, but not
22 always the principal investigator.
23 Q. So of those 5 to 10 clinical trials
24 that you were responsible for designing, how
25

2 many of those were -- involved
3 immunotherapies?
4 A. The majority of them.
5 Q. And which immunotherapies did those
6 involve?
7 A. So as I recall, this is not a
8 comprehensive list, some included
9 pembrolizumab in combination with
10 chemotherapy. I recently did a clinical trial
11 with a drug called camrelizumab. One with a
12 drug called spartalizumab. And I'm the
13 principal investigator of another trial with
14 an immunotherapy whose name I can't recall or
15 pronounce right now.
16 Q. So the clinical trial with
17 camrelizumab, what sort of immunotherapy is
18 that?
19 A. So I misspoke. Camrelizumab is an
20 immunotherapy. I was not the principal
21 investigator of that trial. The one I meant
22 was canakinumab.
23 Q. And what type of immunotherapy is
24 canakinumab?
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25 A. That is an antibody, again,

2 something called IL-1 beta.

3 Q. So not a checkpoint inhibitor?

4 A. Not a checkpoint inhibitor.

5 Q. Okay.

6 A. I -- I -- I don't know if you want

7 background. IL-I beta involves something

8 called MDSCs, or myeloid derived suppressor

9 cells.

10 Q. And you also mentioned a clinical

11 trial involving spartalizumab?

12 A. Correct.

13 Q. What type of immunotherapy is that?

14 A. Spartalizumab is a PD-1 enteron.

15 Q. And do you know who makes that

16 antibody?

17 A. Novartis provided the drug to me

18 for the study, but I think they've given up on

19 or passed it on to someone else.

20 Q. So clinical trials are classified

21 by phases; correct?

22 A. Correct.

23 Q. Okay. And there is a Phase I, a

24 Phase II, and a Phase III?

25 A. And a lot of gray area in between.

2 Q. Okay. What is a Phase I trial?

3 A. So, again, these descriptions are

4 not 100 percent clear-cut, and there is very

5 little that limits a person from describing

6 their trial within one context, even if it

7 crosses a gray area, but traditional Phase I

8 clinical trials were meant to discover whether

9 an agent or a drug is safe and to find a

10 maximum tolerated dose that that drug can be

11 given to to people in a certain circumstance.

12 Q. And what's a Phase II trial?

13 A. So, again, traditionally a Phase II

14 trial was done after a Phase I, when a dose

15 was identified, to try to determine whether

16 there is any evidence of that dose would have

17 a beneficial effect on people or whoever was

18 being tested in that Phase II trial.

19 Q. And what is a Phase III trial?

20 A. So, again, in the most simple

21 terms, a Phase III trial is done if a Phase II

22 trial shows that there is some effect of the

23 medication, to try to determine whether the

24 medication is better than a standard

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25 alternative medication, utilizing a much

1 higher level of statistical significance and
2 standards than in a Phase II.
3 Q. And are Phase III trials generally
4 larger than Phase II trials?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. So, again, it's very hard to give
8 generality for clinical trials, because it
9 would depend on the target and the specific
10 indication and statistical method being used.
11 In many circumstances, Phase III trials are
12 larger, but it's not necessarily the case.
13 Q. And I've seen some labels for sort
14 of intermediate levels. Are you familiar with
15 a Phase IIB trial?
16 A. So, again, these terminology are
17 not defined and people sort of make them up
18 for their own trial. There is an intent.
19 Very often, and not always, a Phase IIB trial
20 would be a Phase II trial where you're trying
21 to determine efficacy, but you do it in a
22 randomized fashion to include some kind of a
23 control group, even though statistically it's
24 not as powerful or as large or as definitive
25

2 as a Phase III trial, but you can get some
3 preliminary data. That is one use of
4 Phase IIB trials. It's not the only use of
5 them.
6 Q. What are some other uses of
7 Phase IIB trials?
8 A. So, again, anyone can call their
9 trial a Phase IIB trial, there is no
10 limitation, but someone might do that if it's
11 sort of a second step they did a Phase II
12 trial, gathered information, but want to
13 gather even more information.
14 Q. And clinical trials can be
15 prospective or retrospective; correct?
16 A. So in general, yes.
17 Q. Okay. And what is a prospective
18 clinical trial?
19 A. So, again, in the simplest terms, a
20 prospective clinical trial is where the
21 patients are identified and being placed on a
22 trial before they are treated, before the
23 question that you're addressing the trial is
24 asked.
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25 Q. And what is a retrospective trial?

A. So one form of retrospective trials is where you look at people who have already been treated and try to analyze the outcomes that they had compared to some other standard.

Q. And is it possible for a clinical trial to be both prospective and retrospective?

A. So this is where the terminology is sort of difficult. In general, no, however, there could be aspects of a trial that were done prospectively and aspects that were done retrospectively.

Q. And how would that work?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I'll give an example from a nontherapeutic clinical trial where this is much more common.

Q. Uh-huh.

A. A group might decide that we want to understand why people under the age of 50 have an increased incidence of colon cancer, and so we enroll 5,000 college students and watch them prospectively to see if they

2 develop colon cancer.
3 20 years later, we take all of that
4 data and we retrospectively go back and look
5 for factors that may contribute to that thing
6 happening. So that's a prospectively
7 collected, retrospectively analyzed trial,
8 that would be considered a very weak trial in
9 our fields.
10 Q. And a clinical trial can be
11 randomized or nonrandomized; correct?
12 A. Again, those are both possibilities
13 in a clinical trial, yes.
14 Q. Okay. What is a randomized
15 clinical trial?
16 A. So there are many ways to
17 randomize, but often a clinical trial that's
18 randomized is a trial in which a patient is
19 enrolled in the trial without anyone or
20 without them knowing what they're going to
21 receive in the trial, and at some point after
22 enrollment, the randomization occurs and
23 they're placed into an arm in that trial.
24 Q. And does that involve randomly
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25 assigning the treatment method that they're

1 going to receive as part of the clinical
2 trial?
3 A. I don't understand the question.
4 Q. So if patients are randomized to
5 different arms, they can be randomized to
6 different methods of treatment, correct, if
7 those arms have different methods of
8 treatment?
9 A. Or no treatment.
10 Q. Or no treatment.
11 ATTORNEY RATLIFF: I object to the form
12 of the question.
13 Q. Are there ways that patients can be
14 randomized that don't implicate the method of
15 treatment in a clinical trial?
16 ATTORNEY RATLIFF: I object to the form
17 of the question.
18 A. I don't think I understand the
19 question.
20 Q. So the example we were talking
21 about is patients being randomized to
22 different arms of a clinical trial where those
23 different arms received different methods of
24 treatment or no treatment; correct?
25

ATTORNEY RATLIFF: I object to the form of the question.

A. So potentially.

Q. Are there other ways other than assigning methods of treatment that patients can be randomized within a clinical trial?

A. Again, I think this is very, very vague.

Q. Uh-huh.

A. I'm not sure I understand what you're referring to.

Q. Well, what are all the ways that patients can be randomized within a clinical trial?

A. So there is no limit to how patients can be randomized. You can randomize patients to whether they go and get the same treatment in one site or another site or whether they have this nurse or that nurse or many, many other things. So the type of treatment is not necessarily what you're randomizing. There could be many other variables, infinite number of variables that could be the randomization variables.

Q. Could a clinical trial be both randomized and nonrandomized?

A. So I think generally a trial that's randomized is described as being randomized. Like I said, there are many variables in a trial. And you certainly can randomize some variables and not others, but that's not usually how we would describe it.

Q. So when a study is referred to as nonrandomized, how would a person of ordinary skill interpret that?

ATTORNEY RATLIFF: Which study are you talking about?

A. I --

ATTORNEY RATLIFF: Hold on.

I object to the form of the question.

A. So can you be specific perhaps about the study or what you're referring to?

Q. Well, you said that a study can be labeled randomized or nonrandomized; correct?

A. (No response.)

Q. How would someone reading a submission on a ClinicalTrials.gov understand that label of randomized or nonrandomized?

1 ATTORNEY RATLIFF: I object to the form
2 of the question.
3 A. So I think a person of ordinary
4 skill in the art would have to look at the
5 information that's in front of them, and I
6 don't think I can answer without seeing the
7 specific information that that person would
8 then utilize to determine whether it's
9 randomized or not randomized.
10 Q. Would that randomization or
11 nonrandomization, would that be limited to
12 assignment to arms in the clinical trial?
13 ATTORNEY RATLIFF: I object to the form
14 of the question.
15 A. I think you already asked that, but
16 again, it really depends on what's written in
17 the document and what the person of ordinary
18 skill would see in front of them to make that
19 determination.
20 Q. What clues would be written in the
21 document that would tell them how randomized
22 or nonrandomized should be interpreted?
23 A. I think we're talking about a
24 theoretical document. If you show me a
25

2 document, I can point to you to what I think
3 would be valid in that document.
4 Q. Well, you mentioned that there
5 could be tons of variables that are randomized
6 within a clinical trial; right?
7 A. Correct.
8 Q. How would a person reading a
9 ClinicalTrials.gov submission related to a
10 trial figure out which variables are
11 randomized and which ones are not?
12 ATTORNEY RATLIFF: I object to the form
13 of the question.
14 A. So a person of ordinary skill would
15 look at the document in front of them, and
16 again, if you give me a specific example, I
17 can look at it and give you my judgment as a
18 person of ordinary skill how they would
19 evaluate that document, but theoretically, I
20 can't answer the question without seeing what
21 you're referring to.
22 Q. Do ClinicalTrials.gov submissions
23 generally contain information on all the
24 possible variables in a given clinical trial?

25 A. Each submission stands on its own.

There is no one rule for all submissions or one general thing that you'd expect. I'd have to evaluate the submission from the framework of a person of ordinary skill to make a determination.

Q. And how would you do that?

A. I would review the submission from the framework of a person of ordinary skill at the time of the relevant question.

Q. And what would you be looking for in that review?

ATTORNEY RATLIFF: I object to the form of the question.

A. I'd be looking at the content of the document.

Q. What sorts of information would you be looking for in the contents of the document?

ATTORNEY RATLIFF: I object to the form of the question.

A. I mean, I would look at everything written in that document. It's hard to answer theoretically without information in front of me that you're asking about.

Q. So in order to have a randomized trial, is it necessary to have at least two different treatment options?

A. Again, it's difficult to answer without understanding a specific trial that you're referring to. As I mentioned earlier, it's conceivable that a trial can randomize patients for something that's not a treatment option. That would be declared clearly or something that would be understood by the person of ordinary skill.

Q. If all arms of a clinical trial receive the same treatment, is it possible to have a randomized trial?

ATTORNEY RATLIFF: I object to the form of the question.

A. So it depends on more specifics of the trial. I think it's hard to answer that question in the abstract. If there are specific examples, I'm happy to review them.

Q. But you're not ruling out that it's possible to have a randomized trial if all arms of a clinical trial receive the same treatment?

A. I didn't rule it out. It depends on what's written in the document and what else is being considered in the clinical trial.

Q. What is the starting point for designing a clinical trial?

ATTORNEY RATLIFF: I object to the form of the question.

A. Can you clarify the question, please?

Q. Well, you designed multiple clinical trials; right?

A. Correct.

Q. What is the impetus for you to start designing the clinical trial?

ATTORNEY RATLIFF: I object to the form of the question.

A. So each one has its own, sorry, impetus and rationale.

Q. Uh-huh.

A. I think in some circumstances we -- I have identified a medication that we think would be beneficial to patients in a certain setting and want to test it on those patients

to see if that confirms the hypothesis.

Q. So you said that each clinical trial has its own rationale; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. I mean, there may be two trials with the same rationale, but each one needs to be judged independently.

Q. Okay. But each clinical trial will have its own rationale; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. You mean there will be a reason why the people are doing the clinical trial?

Q. Essentially, yes.

A. So, yeah, people generally have a reason to do the clinical trials.

Q. Okay. And that rationale is generally related to some sort of hypothesis that they're testing with the clinical trial; correct?

ATTORNEY RATLIFF: I object to the form of the question.

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A. So, again, clinical trials range

from an incredibly broad spectrum of what people are testing and why they're testing it, but every single clinical trial I think is designed to learn some new information that will help us in our knowledge base overall.

Q. And that's based on some sort of rationale for why you would do a clinical trial; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. So generally, yes.

Q. And what are common bases for the rationale for a clinical trial?

ATTORNEY RATLIFF: I object to the form of the question.

A. Do you mean a specific clinical trial?

Q. No, clinical trials in general.

A. I think it's very hard to answer. I'm sorry. There are thousands and thousands of clinical trials. I mean, I could -- do you want to make this concrete, the specific MSI study record that we have here, which

describes the Phase II clinical trial of

2 pembrolizumab in patients with microsatellite
3 unstable tumors, I think this trial
4 specifically was to test whether the response
5 rate and question of the survival would be
6 improved in patients with MSI-high colorectal
7 cancer treated with pembrolizumab.
8 Q. That was not my question.
9 At a general level, can in vitro
10 data serve as a possible rationale for a
11 clinical trial?
12 ATTORNEY RATLIFF: I think that was the
13 response to your question, and also note that
14 the court reporter moved over a second monitor
15 for questioning counselor to see. We are
16 having trouble with the realtime. It stopped
17 over here.
18 ATTORNEY BROWN-MARSHALL: My realtime
19 stopped too.
20 CERTIFIED STENOGRAPHER: Do you want to
21 go off the record?
22 ATTORNEY RATLIFF: Yes, please.
23 ATTORNEY BROWN-MARSHALL: Yes, sir,
24 please.

25 CERTIFIED STENOGRAPHER: Off the

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 stenographic record at 11:05 a.m.
3 - - -
4 (Whereupon, a short recess was
5 taken.)
6 - - -
7 CERTIFIED STENOGRAPHER: Back on the
8 stenographic record at 11:15 a.m.
9 BY ATTORNEY BROWN-MARSHALL:
10 Q. So, Doctor, before we get back to
11 my question that is pending when your counsel
12 unilaterally decided to take a break, I need
13 to ask you: Have you had any conversations
14 with counsel during any of the breaks we've
15 taken today regarding the substance of your
16 testimony?
17 A. No, I've not.
18 Q. So getting back to my question, can
19 in vitro data serve as a possible rationale
20 for starting a clinical trial?
21 ATTORNEY RATLIFF: I object to the form
22 of the question.
23 A. So, again, it's an incredibly broad
24 question, but I -- maybe you can clarify what
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25 you mean by in vitro data as opposed to what?

2 Q. In vitro data as opposed to in vivo
3 data?
4 ATTORNEY RATLIFF: Same objections.
5 A. So I can't speak for every clinical
6 trial, and I think it's possible that someone
7 could submit a rationale to start a trial with
8 in vitro data alone.
9 Q. Okay. And can in vivo animal data
10 serve as the basis for the rationale of a
11 clinical trial?
12 A. Again, it depends on what clinical
13 trial and what stage clinical trial, but there
14 certainly are early stage trials that might be
15 done based on in vivo animal data.
16 Q. And how does the stage of a
17 clinical trial affect the types of data that
18 might serve as the rationale?
19 ATTORNEY RATLIFF: I object to the form
20 of the question, as well as to the premise of
21 the question.
22 A. So as I described earlier, a
23 Phase II clinical trial generally is done
24 after a Phase I clinical trial and thus
25 wouldn't be done without a Phase I clinical

1 trial ahead of it to show a safe and maximum
2 tolerable or effective recommended Phase II
3 dose of a trial.
4 Q. And the Phase I, Phase II,
5 Phase III trials, then those are generally
6 sequential?
7 ATTORNEY RATLIFF: I object to the form
8 of the question.
9 A. So sometimes.
10 Q. Sometimes?
11 A. (Indicating.)
12 Q. When are they not sequential?
13 A. Again, there are no hard rules
14 about a trial, and there are times where a
15 study might do a Phase I and then a Phase III
16 or skip certain steps along the way. It all
17 depends on the context and the findings and
18 the individual details of the trial.
19 Q. What would be the motivation for
20 skipping from a Phase I trial directly to a
21 Phase III trial?
22 ATTORNEY RATLIFF: I object to the form
23 of the question, as well as to the premise of
24 the question.

A. I can't recall right now any specific examples where that was done. I know it has been done, but I think in each circumstance, you have to evaluate why the investigators chose to make that decision.

Q. Have you ever seen a clinical trial that did not have some sort of rationale identified?

A. You mean identified where?

Q. So in the description of the clinical trial?

ATTORNEY RATLIFF: I object to the form of the question.

A. Yeah, I -- I really can't speak to every single clinical trial that I've ever seen, so I can't recall yes or no.

Q. So when conducting a clinical trial, sometimes the rationale is correct and sometimes it's not; right?

ATTORNEY RATLIFF: I object to the form of the question.

A. So what do you mean by rationale being correct or not correct?

Q. So if the clinical trial is testing

a hypothesis based on the rationale, sometimes that hypothesis is correct and sometimes it's not; right?

ATTORNEY RATLIFF: I object to the form of the question.

A. I wouldn't use the word "correct" or "incorrect." I mean, sometimes the hypothesis is confirmed or not confirmed.

Q. Uh-huh.

A. That doesn't change the rationale.

Q. Uh-huh.

But sometimes clinical trials are successful in confirming the hypothesis and sometimes they're not successful in confirming the hypothesis; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. So that is correct in very broad terms. Again, depends on what the hypothesis is when you use the words "correct" or "not correct" or "confirming" or "not confirming."

Q. Do you expect every clinical trial to be successful in confirming the hypothesis that it's testing?

2 A. So it depends on the trial. I
3 would expect to evaluate a clinical trial
4 based on the prior art known before that trial
5 time point when I'm making that assessment and
6 what's available to a person of ordinary skill
7 to determine this likelihood or possibility of
8 success in that clinical trial. It would vary
9 greatly depending on the specifics of the
10 trial and other information in the art and
11 literature.
12 Q. What is the general success rate
13 for clinical trials?
14 ATTORNEY RATLIFF: I object to the form
15 of the question.
16 A. So I don't think one can answer
17 that question, because clinical trials are not
18 one category of things. It really depends on
19 the type of clinical trial, the information
20 that was known prior to the trial, whether it
21 was the first use of a drug or a subsequent
22 use of the drug or a phase of the trial.
23 So I think a specific trial we can
24 potentially give some information, but it
25 always depends on the details of the trial.

Q. And are you aware of any available statistics that had looked at the success rate of clinical trials?

A. So I don't think that it's appropriate to look at clinical trials in general as one category, and I don't think statistics speak for all clinical trials. There are potentially statistics for smaller subsets of that.

Q. So looking at the clinical trials in which you've participated, did you expect all of those clinical trials to be successful?

A. So I can't answer for all of the clinical trials as a group. I think I can speak about specific clinical trials.

Q. Uh-huh.

A. And what information I had going into the trial, what the prior art taught us, and what I would have expected at that time.

Q. Okay. Have you ever participated in a clinical trial where you anticipated that it would fail?

A. Not that I can recall, but I can't specifically recall every single clinical

2 trial I've participated in.
3 ATTORNEY BROWN-MARSHALL: I'd like to
4 mark this as Exhibit 2405.
5 - - -
6 (Whereupon, document entitled
7 Gastrointestinal Cancer - Gastroesophageal,
8 Pancreatic, and Hepatobilia 4042, is received
9 and marked as Exhibit 2405 for
10 Identification.)
11 - - -
12 CERTIFIED STENOGRAPHER: Number 2405.
13 BY ATTORNEY BROWN-MARSHALL:
14 Q. Dr. Oberstein, the court reporter
15 has just handed you Exhibit 2405.
16 Are you familiar with this
17 document?
18 ATTORNEY RATLIFF: And I will object to
19 Exhibit 2405 for the purposes of
20 authentication, foundation, and hearsay.
21 A. Yes, I'm familiar with this
22 abstract.
23 Q. Okay. And what is this abstract?
24 A. So this is an abstract describing a

25 Phase II clinical trial of Lenvatinib plus

2 pembrolizumab for patients with immunotherapy
3 naive advanced gastric cancer following
4 first-line therapy.
5 Q. And you are one of the authors on
6 this abstract; correct?
7 A. That is correct.
8 Q. Okay. And did you participate in
9 the clinical trial described in this abstract?
10 A. Yes, I did.
11 Q. Okay. What was your role in that
12 clinical trial?
13 A. I enroll patients in the clinical
14 trial, and ultimately when the first
15 investigator named here left our institution,
16 I took over her role as the principal
17 investigator for the conclusion of the trial.
18 Q. Okay. And did this specific
19 clinical trial have a rationale?
20 A. Yes.
21 Q. Okay. And what was the rationale
22 for this clinical trial?
23 A. So the rationale of this clinical
24 trial was that treating with -- cancer with a

25 drug that focuses on blood vessels or

2 angiogenesis would make tumors more
3 susceptible to immunotherapy and thus the
4 combination of an antiangiogenic treatment
5 plus immunotherapy treatment would be
6 efficacious.
7 Q. And that rationale was based on
8 preclinical studies; correct?
9 A. It was based on preclinical
10 studies, as well as clinical studies, as this
11 combination is used in other cancers with
12 efficacy.
13 Q. And this clinical trial, you were
14 testing a hypothesis that the combination of
15 VEGF inhibition and ICI may be more beneficial
16 than either agent alone; correct?
17 ATTORNEY RATLIFF: I object to the form
18 of the question.
19 A. So that was the hypothesis in this
20 clinical trial, correct.
21 Q. Okay. And when you say ICI, you're
22 referring to immune checkpoint inhibitors;
23 correct?
24 A. Yes.
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25 Q. And the immune checkpoint inhibitor

1 that you tested in this trial was
2 pembrolizumab; correct?
3 A. That is correct.
4 Q. What was the result of this
5 clinical trial?
6 A. So this clinical trial it would
7 describe here was designed to determine
8 whether we can achieve a response rate of
9 20 percent or so.
10 And ultimately, we had to stop the
11 trial before we finished it because the
12 standard of care of treatment for gastro
13 cancer changed during the course of the trial.
14 So we did not get complete results
15 from the trial, but the preliminary result of
16 those 24 patients who were enrolled were that
17 20 percent of them responded to treatment, but
18 that was less than what we were anticipated
19 seeing because we had to stop the study early.
20 Q. And for this study, it did not meet
21 the primary endpoint in ICI-naive cancers;
22 correct?
23 ATTORNEY RATLIFF: I object to the form
24 of the question.
25

2 A. That is correct.

3 Q. Why were you testing in ICI-naive

4 patients?

5 A. Because at the time we started this

6 study, there was no FDA approval or wide use

7 of immune checkpoint inhibition in first-line

8 treatment of gastric cancer.

9 Q. So why would that motivate you to

10 test in ICI-naive patients?

11 A. Because we suspected that should we

12 move forward with this combination, that's who

13 would get it. We wanted to have a relevant

14 patient population.

15 Q. So for this specific study, when

16 you started this study, did you anticipate

17 that it would be successful?

18 A. So as I clarified, I was not

19 involved in starting this study. I came into

20 the study in the middle of the course of the

21 study.

22 Q. Uh-huh.

23 A. But -- so I can't answer for the

24 person who started the study.

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25 Q. So at the point that you joined the

1 study, did you anticipate the study would be
2 successful?
3 A. I did.
4 Q. You can put that aside.
5 ATTORNEY BROWN-MARSHALL: So I'm
6 handing the court reporter an exhibit that I
7 would like to mark as 2406.
8 - - -
9 (Whereupon, document headed HHS
10 Public Access, is received and marked as
11 Exhibit 2406 for Identification.)
12 - - -
13 CERTIFIED STENOGRAPHER: Number 2406.
14 BY ATTORNEY BROWN-MARSHALL:
15 Q. Dr. Oberstein, are you familiar
16 with this exhibit?
17 ATTORNEY RATLIFF: I will object to
18 Exhibit 2406 for the purposes of
19 authentication, foundation, and hearsay.
20 A. Yes, I'm familiar with this
21 publication.
22 Q. Okay. And are you an author on
23 this publication?
24 A. Yes, I am.
25

2 Q. What is this publication?

3 A. So this publication describes the

4 results from a Phase IIB randomized

5 multicenter study of something called GVAX

6 pancreas vaccine and CRS207, compared with

7 chemotherapy in adults previously treated with

8 metastatic pancreatic adenocarcinoma.

9 Q. And the first author of this

10 publication is Dung Le; correct?

11 A. That is correct.

12 Q. And did you work with Dr. Le during

13 the course of this clinical trial?

14 A. Yes.

15 Q. Have you worked with Dr. Le before?

16 A. So just to clarify, when you say

17 "worked with," we participated on group calls

18 together to discuss the progress of the trial.

19 Q. Uh-huh.

20 A. I participated on calls with Dr. Le

21 before this, yes.

22 Q. Okay. And what was your role in

23 this trial?

24 A. So I as I recall was a principal

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25 investigator of this trial at my site, which

1 was at Columbia at the time.
2 Q. Okay. And were you involved in the
3 design of this clinical trial?
4 A. I don't recall my exact role in the
5 design of the trial. I don't recall. So I
6 may have been, but I can't recall.
7 Q. Okay. Was Dr. Le involved in the
8 design of this clinical trial?
9 A. I can't speak for Dr. Le.
10 Q. Okay. And this trial tested GVAX
11 pancreas and CRS207, compared with
12 chemotherapy in adults with previously treated
13 metastatic pancreatic adenocarcinoma; correct?
14 A. That is correct.
15 Q. What is GVAX pancreas?
16 A. So GVAX pancreas is a type of a
17 vaccine that is injected into patients and
18 meant to stimulate an immunoresponse against
19 their tumor.
20 It specifically stimulates
21 something called granulocyte macrophage colony
22 stimulating factor secreting --
23 - - -
24 (Clarification requested by the
25

1 stenographer.)
2 A. CSF for colony stimulating factor
3 secreting tumor cells from pancreatic cancer
4 cell lines to induce an immunoresponse in the
5 patient.
6 Q. So you would consider GVAX pancreas
7 as a type of immunotherapy?
8 A. I would say it's a type of vaccine,
9 so it depends on how you qualify
10 immunotherapy. It's not a checkpoint therapy,
11 but it's certainly something that is meant to
12 stimulate the immune system.
13 Q. Well, would you categorize GVAX
14 pancreas vaccine as an immunotherapy?
15 A. Again, I think generally we think
16 of it as a vaccine therapy, which is possibly
17 a subset, but not usually classified as
18 immunotherapy.
19 Q. So you don't consider vaccines to
20 be a subset of immunotherapies?
21 ATTORNEY RATLIFF: I object to the form
22 of the question.
23 A. I don't think there is a standard
24 definition. I think very often when people
25

1 talk about immunotherapy for cancer, they're
2 referring to immune checkpoint therapy or
3 immune stimulatory therapy, not vaccine
4 therapy, which gets its own sort of
5 classification, but vaccines do work by
6 affecting the immune system.
7 Q. What was the rationale for the
8 clinical trial in Exhibit 2406?
9 A. I can't definitively speak to that
10 because I was not the primary person who
11 designed the trial.
12 Q. What was your understanding of the
13 rationale?
14 A. So my understanding, again, this is
15 my recollection years later, is that this was
16 a vaccine that Hopkins was developing for use
17 in pancreatic cancer, and they had had very
18 little success with it overall over many
19 years, except in two people who were on a
20 different clinical trial, who received this
21 other medication called CRS207, who received
22 that medication, coincidentally went on a
23 clinical trial with the vaccine and then
24 seemed to do quite well. So they hypothesized

2 that there was some connection between those
3 two things.
4 Q. And that was based on the results
5 of those two patients?
6 A. That's my recollection.
7 Q. Okay.
8 A. I was not involved with treating
9 those patients and those studies were not done
10 with my supervision.
11 Q. And this article talks about
12 CRS207, what is that?
13 A. So CRS207 is basically a live
14 bacteria. So you inject bacteria into
15 patients. It's attenuated so that it doesn't
16 cause severe illness, but it causes them to
17 get pretty sick because it is live bacteria,
18 and the hope and expectation is that that will
19 cause their immune system to target the
20 bacteria and also target the cancer.
21 Q. So is CRS207 then given in
22 conjunction with the GVAX pancreas vaccine in
23 this clinical trial?
24 A. So there were three arms in this

25 clinical trial. Arm 1 got a combination of

2 the GVAX pancreas vaccine in CRS207; Arm 2 got
3 CRS207 alone without the vaccine; and Arm 3
4 received chemotherapy.
5 Q. And what were the results of this
6 clinical trial?
7 A. So the results of the clinical
8 trial were that the overall survival in the
9 true group that got GVAX plus CRX207 was not
10 different than those who got chemotherapy. So
11 it was not improved as had been hypothesized.
12 Q. So the study failed to meet its
13 primary efficacy endpoint; correct?
14 A. That is correct.
15 Q. And when you joined the study, did
16 you anticipate that the study would be
17 successful?
18 A. Yes, I did.
19 Q. And that was based on the data
20 related to the treatment of the two
21 patients --
22 A. There was additional data as well.
23 So prior to this Phase IIB study, they
24 conducted a 2A study where they gave similar

25 treatments to look at different doses that

1 might be effective.
2 Q. Okay.
3 A. I was not part of the study, but I
4 knew the data from it.
5 Q. So the rationale was based on those
6 two patients that were treated at Johns
7 Hopkins and had a successful response and
8 results of that Phase IIA study; correct?
9 ATTORNEY RATLIFF: I object to the form
10 of the question, as well as to the premise of
11 the question.
12 A. So I believe so.
13 Q. Okay. And in spite of that
14 promising data, the study still failed to meet
15 its primary endpoint?
16 A. So I would say despite that
17 preliminary data.
18 Q. It still failed to meet its primary
19 endpoint?
20 A. This study did fail to meet its
21 primary endpoint, correct.
22 Q. You can put that aside.
23 So as part of your work designing
24 and conducting clinical trials, do you have
25

2 any experience with the ClinicalTrials.gov
3 website?
4 A. What do you mean by "experience"?
5 Q. Have you ever made submissions to
6 ClinicalTrials.gov in conjunction with a
7 clinical trial that you either designed or
8 conducted?
9 A. Yeah, yes, but I didn't personally
10 make the submissions. We have a regulatory
11 coordinator who does the submissions. I have
12 to approve them if they're done for my trial.
13 Q. Okay. Are you involved in drafting
14 those submissions to ClinicalTrials.gov
15 A. I certainly approve them before
16 they're posted.
17 Q. But you have a team that assists
18 you in drafting and actually posting them?
19 A. We definitely have a team that's
20 part of our regulatory control to make sure we
21 do everything we have to do before starting
22 the study.
23 Q. Are submissions to
24 ClinicalTrials.gov required for human clinical
25 trials?

A. In the U.S.?

Q. In the U.S., yes.

A. I believe so, yes.

Q. Okay. And FDA does not pay investigators for making submissions to ClinicalTrials.gov; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. I'm really not familiar with FDA payments.

Q. Okay. You've never received a payment from the FDA for making a submission to ClinicalTrials.gov

A. I don't think I've ever received any payment from the FDA. I don't -- I don't know if -- there might be a charge to post. I really don't know.

Q. Do you agree that submissions to ClinicalTrials.gov provide important information to the public?

A. I do agree with that.

Q. And as a result, those submissions must include certain basic information about the clinical trial; correct?

A. So I think the submission -- the data that's required in ClinicalTrials.gov is determined by the FDA.

Q. Uh-huh.

A. Not by the public.

Q. Uh-huh.

But I'm not asking about who determines what needs to be included. Let me rephrase this.

In order for the public to have access to the information in ClinicalTrials.gov -- strike that.

In order for the public to have access to important information about clinical trials, the submissions to ClinicalTrials.gov need to contain that sort of basic important information; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I think that the investigator and their team determine what to include in their submission to ClinicalTrials.gov. Again, it's not determined based on the public. It's based on their motivation.

1 There are requirements in certain necessary
2 fields, but there is certainly leeway for the
3 investigator to add information or include
4 information based on what they want to do.
5 Q. So how does the public use the
6 information that's posted on
7 ClinicalTrials.gov
8 ATTORNEY RATLIFF: Every single person
9 in the world you're asking about?
10 A. Sorry, so can you clarify what you
11 mean by that?
12 Q. Well, you agreed that submissions
13 to ClinicalTrials.gov provide important
14 information to the public; correct?
15 A. Yes, I agree with that.
16 Q. Okay. So how is that information
17 used by the public?
18 ATTORNEY RATLIFF: I object to the form
19 of the question.
20 A. So that's overly broad I would say
21 because the public can encompass many, many
22 people who are using it for many different
23 purposes.
24 Q. Uh-huh.
25

A. One purpose of people using ClinicalTrials.gov would be to understand whether there is a trial that they can participate in that would fit their tumor type that's currently enrolled in.

Q. Uh-huh.

A. There are many other potential ways that the public would use this information.

Q. Would you say that gaining information about potential clinical trials is the primary purpose for giving the public access to ClinicalTrials.gov information?

A. I don't know that there is a primary purpose. It would depend on the person submitting the submission to ClinicalTrials.gov and what they wanted to include in that submission --

Q. Uh-huh.

A. -- to help or not help the public or anybody else who is looking at the submission.

Q. Does NYU, where you're employed, does it have any requirements around

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submissions to ClinicalTrials.gov for the

1 purposes of the clinical trials that you work
2 on?
3 A. You mean in addition to the federal
4 requirements or separate from that?
5 Q. Do they have any requirements at
6 all in conjunction with submissions to
7 ClinicalTrials.gov
8 A. So I believe that we have a
9 requirement that a trial be submitted on
10 ClinicalTrials.gov before it can be opened and
11 enrolling patients.
12 Q. So if a clinical trial involves a
13 new drug or a new use for a known drug, you'll
14 need to submit an IND; correct?
15 ATTORNEY RATLIFF: I object to the form
16 of the question.
17 A. So I don't recall the exact
18 requirements for when to submit an IND. I do
19 recall the FDA has a very extensive website of
20 the checklist that one fills out to determine
21 whether their new study needs an IND. It's
22 not as simple as I think you just put it.
23 Q. Okay. Let's back up.
24 What is an IND?
25

A. So the words IND stands for Investigational New Drug Application.

Q. Okay. And those INDs are submitted to FDA; correct?

A. Correct.

Q. Okay. Who submits the IND to FDA?

ATTORNEY RATLIFF: I object to the form of the question.

A. So the IND holder, if that answers -- I'm not sure I understand the question either.

Q. So on a clinical trial, who is the person on the team who generally submits the IND to FDA?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. So I think it varies very much depending on what kind of trial, who is involved in the trial, you know, there could be many different workflow in IND within a clinical trial. Someone has to take that responsibility and is responsible for

submitting the required documents to the FDA

2 to get approval prior to the trial being able
3 to proceed.
4 I'm sorry, let me correct that.
5 Not so much the trial. Prior to the
6 investigation being able to proceed.
7 Q. Is the IND holder generally a
8 physician who's participating in the clinical
9 trial?
10 A. It varies greatly depending on the
11 nature of the trial. Not necessarily.
12 Q. Who else might be the IND holder
13 for a clinical trial?
14 A. So other parties of the trial, such
15 as the sponsor of the trial or pharmaceutical
16 company or a clinical research organization
17 that's organizing the trial can all be IND
18 holders as far as I understand.
19 Q. And IND submissions made to FDA are
20 confidential submissions; correct?
21 A. I'm not sure.
22 Q. Okay. Are you aware of any ways in
23 which FDA makes IND submissions publicly
24 available?
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25 A. I'm not aware of any such ways.

2 Q. Are you the IND holder for any
3 clinical studies?
4 A. Yes.
5 Q. Okay. Which ones?
6 A. Do you have my CV? Maybe that
7 would help. Well, just for one example, that
8 study you presented earlier, this study
9 (indicating).
10 Q. Uh-huh.
11 A. I'm IND holder for this study.
12 Q. And you are holding up
13 Exhibit 2405; correct?
14 A. 2405, correct.
15 Q. So you weren't the IND holder --
16 A. I didn't submit the IND because as
17 I said, I took over the study. Someone left
18 the institution. I stepped into that role.
19 So by stepping into that role, I became the
20 IND holder, and it's my responsibility to
21 submit reports to the FDA about progress and
22 data about the study.
23 Q. Okay. Have you ever prepared an
24 IND for submission to the FDA?
25 A. Yes, I have.

Q. And have you reviewed INDs for studies you participated in, but you were not the IND holder?

A. I don't recall that, but it's possible.

Q. Is it customary for a physician who's participating in a clinical trial, who is not the IND holder, to review those IND submissions?

ATTORNEY RATLIFF: I object to the form of the question.

A. I think it depends on the trial and the specific circumstances of that.

Q. And FDA must approve IND submissions before a clinical trial can start; correct?

A. So essentially the FDA has to give the okay to move ahead with the trial after the IND submission.

Q. And IRB approvals are also required before a clinical trial can start; correct?

A. So in almost every single institution in the United States, IRB approval is required.

Q. An IND holder for a new use for a known drug may not necessarily be the IND holder for the underlying drug; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. So, again, an IND is not for a drug. It's for an investigation.

Q. Uh-huh.

So if an investigation is looking at a new use for a known drug, there is a separate IND for that investigation and a separate IND for the underlying drug; correct?

A. So --

ATTORNEY RATLIFF: I -- I object to the form of the question.

A. So potentially, as I said earlier, there are certainly circumstances where a study can be IND exempt and you don't need to get an IND if one was already obtained for the same drug in some circumstances.

Q. And what are the situations in which an investigation would be IND exempt?

A. So, as I said, I can't recall them off the top of my head. I know that the FDA

2 has a long list. It's essentially a checklist
3 that we go through to determine if your study
4 is IND exempt or requires an IND.
5 Q. So in the INDs that you have
6 reviewed, have you ever seen statements
7 informing FDA that the IND holder did not
8 think the study was going to work?
9 A. So I have submitted IND statements
10 to the FDA and I have never submitted that. I
11 can't speak for other people's IND
12 submissions.
13 Q. Clinical trials may involve the
14 evaluation of a biomarker; correct?
15 A. In general, that is correct.
16 Again, very vague, but correct.
17 Q. Okay. And what is a biomarker?
18 A. So a biomarker, again, is quite a
19 vague term, but it's something that is
20 biologically or related to a tumor or a person
21 that gives some information about how they
22 will do or how they will respond to a therapy.
23 Q. And there are different types of
24 biomarkers; correct?
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25 ATTORNEY RATLIFF: I object to the form

1 of the question.
2 A. What do you mean by the question?
3 Q. So biomarkers can serve different
4 purposes; correct?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. I'm not sure what you're referring
8 to. I'm sorry.
9 Q. So are you familiar with the term
10 "predictive biomarker"?
11 A. I'm familiar with the term, yes.
12 Q. Okay. What is a predictive
13 biomarker?
14 A. So a predictive biomarker, again,
15 like all these terminology, can mean different
16 things in different settings, and so it would
17 be helpful to see the exact context you're
18 using it in.
19 In general, or sometimes people use
20 it to be a prediction about whether a
21 treatment or an intervention will help a
22 person.
23 Q. And have you been involved in any
24 clinical trials that evaluate a predictive
25

2 biomarker?

3 A. So I've been involved in many, many

4 trials. I can't recall specifically.

5 Q. But sitting here today, you can't

6 remember any clinical trial that you've been

7 involved in that involved the evaluation of a

8 predictive biomarker?

9 A. I think sitting here today, I don't

10 have recollection right now.

11 Q. How many predictive biomarkers have

12 been identified in conjunction with oncology

13 therapies?

14 A. Again, that's a very broad

15 question, and I think pretty much beyond the

16 scope of what I was asked to evaluate here. I

17 think there are many, but I can't give you a

18 specific number. Oncology is a very broad

19 field encompassing many tumors, many trials,

20 many possible biomarkers, and I think there

21 are many of them, but I can't recall every

22 single one.

23 Q. And some predictive biomarkers will

24 work in one type of cancer, but not in another

25 type of cancer; correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. Can you refer to a specific biomarker to ask that question?

Q. No, I'm just asking in general.

ATTORNEY RATLIFF: Then I object to the in general asking a question.

A. So it's hard to answer without a specific example as to what exactly you mean by that.

Q. In your practice with your GI oncology patients, do you have them evaluated for a certain set of biomarkers?

A. Again, it's a very broad question. You mean all GI cancer patients in all settings?

Q. Let's start with colorectal cancer patients. Do you have your colorectal cancer patients evaluated for a certain set of biomarkers?

A. So depends on the stage of the colon cancer and many other features with the patient. Sometimes I do.

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Q. Okay. And when you do that, what

1 sort of testing do you perform on those
2 colorectal cancer patients?
3 A. I'm sorry, can you clarify what you
4 mean by that?
5 Q. So one way to test patients for
6 biomarkers is to have their tumor more
7 sequenced; correct?
8 A. That's correct.
9 Q. Okay. And when their tumor is
10 sequenced, they're looking for the presence of
11 certain biomarkers; correct?
12 ATTORNEY RATLIFF: I object to the form
13 of the question.
14 A. There are many reasons to sequence
15 a tumor. One of them may be to identify
16 biomarkers, but there are many other reasons
17 you may do it.
18 Q. What sort of biomarker-related
19 testing do you order for your colorectal
20 cancer patients?
21 A. So, again, some of it depends on
22 the particular stage of the patient and their
23 treatment options and whether this information
24 is going to change what we do for the patient.
25

2 Some of the biomarkers that we look at are
3 based on immunohistochemistry.
4 Some are based on PCR testing or
5 next generation sequencing testing are the
6 primary ways. We also utilize blood testing
7 for many of those biomarkers, not tumor
8 testing.
9 Q. And roughly, how many biomarkers do
10 you have tested for your colorectal cancer
11 patients?
12 A. Again, it's really hard to answer a
13 general question. It depends on the person
14 and the stage and the sample that's available
15 for us. It can range from a very small
16 number, to a very large number based on those
17 factors.
18 Q. Okay. Ballpark, what is the very
19 large number that you might be looking at?
20 A. So when we do next generation
21 sequencing, our panel generally looks at 500
22 genes. Those are really the spectrum of all
23 the genes that anyone who's ever had interest
24 in.
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25 The ones that might be relevant for

our patients are probably limited to 30 to 50, but it depends on the circumstance, and, of course, there are things that we discover as time goes on.

Q. Are you familiar with a term "treatment selection marker"?

A. Not particularly. It sounds like something, but I don't think I've heard it before.

Q. So if a treating oncologist is interested in the results of a clinical trial, how would they learn those results?

ATTORNEY RATLIFF: I object to the form of the question.

A. So some of it would depend on who's running the clinical trial and how they found out that the trial even happened.

Q. Uh-huh.

A. One could reach out to the contact person for a trial and ask for information. Very often clinical trial results are posted online or presented in conferences.

Of course, it happens that

something is presented and nobody knows about

it or you didn't personally know about that, so you might have to do a literature search and look for the results of that trial.

Q. When you say that the results might be posted online, is that a posting on ClinicalTrials.gov

A. That's one way to post things online. There is other ways to publish things.

Q. Okay. What other means of publishing clinical trial results online are available?

ATTORNEY RATLIFF: I object to the form of the question.

A. So trials can be presented to conferences and those abstracts are posted publicly or submitted for manuscript publication, which would get it posted, and to be very honest, nothing stops a person running a trial, who is running a trial, from just putting on Twitter the results of their trial.

Q. Uh-huh.

A. Every day if he wants.

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Q. And if a -- so if a researcher

1 posts the results of a clinical trial to
2 ClinicalTrials.gov, those will appear in the
3 study record; correct?
4 ATTORNEY RATLIFF: I object to the form
5 of the question.
6 A. What do you mean by "the study
7 record"?
8 Q. So on ClinicalTrials.gov, there are
9 multiple tabs, one of which is the study
10 record tab; correct?
11 A. I don't recall exactly what it
12 looks like online.
13 Q. Does ClinicalTrials.gov post
14 submissions related to the study record of a
15 clinical trial?
16 A. What do you mean by "post
17 submissions"?
18 Q. ClinicalTrials.gov is a website?
19 A. Correct.
20 Q. Researchers make submissions to
21 ClinicalTrials.gov that are then posted on
22 that website; correct?
23 A. That's correct.
24 Q. Okay. And one of the references
25

1 that you rely on in formulating your opinions
2 is something that you refer to as the MSI-high
3 study record; correct?
4 A. That is correct.
5 Q. So that is a June 10, 2013
6 submission of a version of a study record to
7 ClinicalTrials.gov; correct?
8 ATTORNEY RATLIFF: Are you representing
9 that to him?
10 ATTORNEY BROWN-MARSHALL: I'm asking
11 him.
12 ATTORNEY RATLIFF: I object to the form
13 of the question.
14 A. So the MSI-high study record that I
15 referred to throughout my declaration is the
16 one that I have that's posted on June 10,
17 2013, is ClinicalTrials.gov.
18 BY ATTORNEY BROWN-MARSHALL:
19 Q. Okay. And you can see from
20 Exhibit 1005 that there are multiple
21 submissions underneath that study record;
22 correct?
23 A. That is correct.
24 Q. Okay. So I'm asking when a
25

1 researcher posts the results of a clinical
2 trial to ClinicalTrials.gov, are those
3 included as a submission in the study record
4 for that clinical trial?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. So I suspect that they are.
8 Q. Uh-huh.
9 A. When one goes online to
10 ClinicalTrials.gov, there are tabs, which is
11 what I thought you were referring to, and
12 there is a separate tab now for study results.
13 Q. Okay.
14 A. I don't think it existed in 2015.
15 Q. Okay.
16 A. But I would have to confirm that.
17 Q. Okay. But now you think that you
18 can go to ClinicalTrials.gov and click on a
19 results tab and it will show you the results
20 of the clinical trial?
21 A. If the investigators have posted
22 the results.
23 Q. Okay. At what point would a
24 treating oncologist rely on the results of a
25

2 clinical trial in making a treatment decision
3 for one of their patients?
4 ATTORNEY RATLIFF: I object to the form
5 of the question.
6 A. So that strongly depends on the
7 nature of the clinical trial, the results of
8 the trial, and what was known in the prior art
9 to that treating oncologist at the time that
10 they're making that decision.
11 Q. Would they wait until results of
12 the clinical trial are available to make a
13 decision to treat one of their patients based
14 on that method?
15 ATTORNEY RATLIFF: I object to the form
16 of the question.
17 A. As I stated, it depends on what was
18 available to that oncologist in the prior art
19 and what other information they have to make a
20 determination.
21 Q. So that would be based on the
22 publicly available information that that
23 treating oncologist could access?
24 ATTORNEY RATLIFF: I object to the form

25 of the question.

2 A. Is that something different than
3 the prior art?
4 Q. Well, you used the term "prior
5 art," and is it your understanding that prior
6 art is publicly available?
7 A. Yes, it is.
8 Q. Okay. So if you're using the term
9 "prior art," does that necessarily mean that
10 the information that the treating oncologist
11 is relying on is publicly available?
12 ATTORNEY RATLIFF: And by "treating
13 oncologist," are you referring to every
14 oncologist in the world?
15 ATTORNEY BROWN-MARSHALL: I'm referring
16 to a treating oncologist.
17 ATTORNEY RATLIFF: Oh. I object to the
18 form of the question.
19 A. So depending on the context and
20 this person of ordinary skill who might be
21 your treating oncologist, they would evaluate
22 the information that's available to them in
23 the prior art to make a decision as to whether
24 or not to utilize the treatment.
25

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1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 BY ATTORNEY BROWN-MARSHALL:
3 Q. When a researcher is conducting a
4 clinical trial, does statistical significance
5 play a role in assessing the results of that
6 trial?
7 ATTORNEY RATLIFF: I object to the form
8 of the question.
9 A. So, again, it's a very broad
10 question and will depend on the specific
11 trial --
12 Q. Uh-huh.
13 A. -- what the results are; what
14 statistics were planned for the trial; and
15 what else is known in the prior art, probably
16 among other things.
17 Q. Uh-huh.
18 A. But I think it's really hard to
19 describe a general principle that will be true
20 about all clinical trials, and we need to talk
21 about a specific trial to answer that.
22 Q. How do you determine if a clinical
23 trial has met its primary endpoint?
24 ATTORNEY RATLIFF: I object to the form
25 of the question.

A. When you say "you," who are you referring to?

Q. A researcher designing the clinical trial?

ATTORNEY RATLIFF: The same objection.

A. So for the most part, clinical trials should have objectives that are clearly stated and well-defined, and it's either yes or no whether you meet those objectives.

There are certainly times where there are multiple objectives in a trial and you meet one and not the other and then you have to evaluate what the significance of that is, and there are certain times where a person of ordinary skill reading the trial, even if it did not or did meet its -- reached their primary objective, will determine to utilize that information or not utilize that information in how they behave and treat patients.

Q. When designing a clinical trial, is the power of the trial something that a researcher would take under consideration?

ATTORNEY RATLIFF: I object to the form

2 of the question.
3 A. Again, it's very difficult to give
4 an answer that is true for every investigator
5 for every clinical trial. I think if you
6 speak to a specific clinical trial, usually
7 power has an impact.
8 For example, in the MSI study
9 record, like this is a trial that was designed
10 to evaluate pembrolizumab in patients with
11 microsatellite unstable tumors. The
12 statistics that went into this trial would
13 incorporate the power of whatever decision was
14 ended up being discovered in the trial.
15 Q. When we talk about "power," what
16 does that mean?
17 A. Power is a statistical term, and it
18 generally describes the likelihood that the
19 response that you receive is actually an
20 accurate response, and you can have basically
21 a false negative, missed true answer.
22 Q. And is it possible to design a
23 clinical trial powered to one patient?
24 A. I'm not sure.
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25 Q. So if you would, Dr. Oberstein, in

2 your declaration, back to Paragraph 10, so in
3 the first sentence you say: My research
4 activities that have focused on designing and
5 conducting clinical trials is a novel agents,
6 including immunotherapies for the treatment of
7 colorectal and pancreatic and other GI cancer
8 patients.
9 What do you mean by
10 "immunotherapies"?
11 A. So that in that sentence, I mean a
12 very broad term of any therapy that modifies
13 the immune system in order to affect cancer
14 outcomes.
15 Q. Okay.
16 A. And so it can incorporate
17 checkpoint therapies, other checkpoints
18 besides the PD-1, PD-L1 that are well-known.
19 We also, as I said earlier, are
20 doing studies that are called myeloid
21 checkpoints essentially or myeloid immune
22 suppressive cells. I am doing some studies
23 with vaccines, and I'm looking at other
24 components of the immune system.
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25 Just to add one last detail: I'm

1 actually doing a trial now where we're having
2 patients exercise to see if that enhances
3 their immune system.
4 Q. Interesting.
5 A. So in theory, that counts as
6 immunotherapy.
7 Q. So immunotherapy is a category that
8 encompasses checkpoint inhibitors, monoclonal
9 antibodies, vaccines, and even exercise?
10 ATTORNEY RATLIFF: I object to the form
11 of the question.
12 A. So, again, like I said before, it
13 really depends on the context and how someone
14 is using it.
15 Q. Uh-huh.
16 A. And there are certainly very
17 specific understandings within the literature
18 where someone meets it one way or the other, I
19 think a person of ordinary skill would have to
20 evaluate each reference in its context.
21 Q. Okay. You mentioned immune
22 checkpoint inhibitors. How many different
23 types of immune checkpoint inhibitors are used
24 in immunotherapy for oncology?

2 A. So I don't think I'm qualified to
3 speak about all oncology. There are many,
4 many cancers that are outside of my expertise.
5 Q. Uh-huh.
6 A. Within GI cancers, we primarily use
7 two checkpoints right now, CTLA4 and PD-1.
8 There are many ways to target those
9 checkpoints, so there are multiple different
10 drugs. Those are the two that are currently
11 approved for GI cancers.
12 Q. Are --
13 A. There are other checkpoints in
14 other cancers and there are many clinical
15 trials looking at other points.
16 Q. And do you have some examples of
17 those other checkpoints inhibitors that are
18 used in other cancers?
19 A. So LAG-3 is one of the examples.
20 Q. Uh-huh.
21 Are PD-L1 checkpoint inhibitors
22 available?
23 A. Yes.
24 Q. Okay. Are there any other types of
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25 checkpoint inhibitors that are available that

2 you're aware of?

3 A. So I'm not aware of any others that

4 are FDA approved. Again, there are many in

5 clinical trials that I can't necessarily

6 comment on or remember today.

7 Q. Okay. Is T-cell transfer

8 considered a type of immunotherapy?

9 A. So, again, this falls into the

10 categories of how you define things.

11 Q. Uh-huh.

12 A. It depends on what the context is.

13 Q. Uh-huh.

14 A. So it certainly is not a checkpoint

15 blockade and nothing to do with that

16 checkpoint part of the immune system.

17 Q. Uh-huh.

18 A. It -- certainly T-cells are part of

19 the immune system, and by giving activated

20 T-cells, which is one way of T-cell transfer,

21 you can stimulate the immune system.

22 Q. Is T-cell transfer a therapy that

23 is used in oncology?

24 A. So, again, I think it's outside of

25 the scope of my expertise. In GI cancers,

it's not a therapy that's used. There are certainly what are called CAR-T cells and something called TILs that are approved in other cancers that are not GI cancers.

Q. I think you mentioned before that monoclonal antibodies are considered a type of immunotherapy; is that correct?

A. So it depends on what they target. Monoclonal antibodies are targeted agents. If they target the immune system, they can be a type of immunotherapy.

Q. Okay. So what types of targeted monoclonal antibodies are available for oncology?

A. Overall?

Q. Well, let's start with GI cancers and then go broader.

A. So there are many different types of monoclonal antibodies. I'm not sure if you want a list of all the targets?

Q. List the ones that you're aware of.

A. So EGFR targeted antibodies; VEGF. There are new antibodies that target something called Claudin CLDN18.2.

2 Q. Uh-huh.

3 A. There are others.

4 Q. Is oncolytic virus therapy

5 considered a type of immunotherapy that's used

6 in oncology?

7 A. So oncolytic virus therapy, if it's

8 meant to stimulate the immune system,

9 certainly could be considered a type of

10 immunotherapy.

11 Q. And is that used in GI cancers?

12 A. It is not. Outside of clinical

13 trials.

14 Q. Okay. But you're aware of

15 oncolytic virus therapy being used in clinical

16 trials for GI cancers?

17 A. I'm aware of one trial that I

18 participated in that we utilized oncolytic

19 virus therapy in pancreatic cancer.

20 Q. Are -- immune system modulators,

21 are those considered immunotherapies for

22 oncology?

23 A. So, again, immunomodulators could

24 be a type of immunotherapy.

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25 Q. And in the category of immune

2 system modulators, that can include cytokines;
3 correct?
4 A. Cytokines, yes.
5 Q. Okay. And cytokines include
6 interferons and interleukins?
7 A. Among many others, yeah.
8 Q. How many cytokines are available
9 for oncology therapy?
10 A. So none of these are approved for
11 GI cancers.
12 So I don't have a specific answer
13 for you. There are many, many cytokines that
14 are potential targets for cancer therapy.
15 Q. Okay. Is BCG also a type of immune
16 system modulator?
17 A. Yes.
18 Q. Okay. And that is Bacillus
19 Calmette-Guerin?
20 A. I don't think anyone has ever said
21 something besides BCG.
22 Q. And what is BCG?
23 A. BCG is a -- essentially a live
24 virus that is injected -- or bacteria, sorry,

25 that's injected to stimulate an immune -- an

2 immune response and it's utilized in nonGI
3 cancers.
4 Q. What about immunomodulatory drugs,
5 are those a type of immunotherapy?
6 A. So anything that modulates the
7 immune system is, and again, they're not
8 utilized generally in GI cancers. And for the
9 most part, they're not used in cancers.
10 They're used in other diseases. Well out of
11 the scope of my expertise for the record.
12 Q. Yeah.
13 Would VEGF inhibitors be considered
14 an immunomodulatory drug?
15 A. So I listed them early as
16 monoclonal antibiotics, as you recall. So
17 generally, we would not consider them
18 immunomodulatory.
19 As you detailed before in
20 Exhibit 2405, that was one of the hypotheses
21 of our study, is that they might have that
22 role.
23 As you said, we really weren't able
24 to conclude that, and so we don't know for

25 sure.

2 THE WITNESS: Break?

3 ATTORNEY RATLIFF: Sure, Doctor. Want

4 to break for lunch?

5 THE WITNESS: Good time for a break for

6 lunch I think? We've been going for an hour.

7 ATTORNEY BROWN-MARSHALL: Actually, I

8 may have one or two more questions.

9 ATTORNEY RATLIFF: It's up to you,

10 Doctor.

11 THE WITNESS: It's okay with me to do

12 one or two more.

13 BY ATTORNEY BROWN-MARSHALL:

14 Q. So, Dr. Oberstein, would you agree

15 with me that the term "immunotherapy" covers a

16 broader range of treatments than just immune

17 checkpoint inhibitors; correct?

18 ATTORNEY RATLIFF: I object to the form

19 of the question.

20 A. So as I've said several times, I

21 think the term depends on the context in which

22 it's used in a specific setting.

23 Within a sentence, within a context

24 to a person of ordinary skill, it might mean

25 they currently used immunotherapies, which are

1 primarily checkpoint blockade. It could mean
2 something different, but it all depends on the
3 context in which that word is used.
4 Q. So you would look to the context
5 surrounding the word to understand what the
6 term "immunotherapy" would mean?
7 A. I would do more than that. I would
8 look to the context surrounding the word and
9 what the person reading that word knows about
10 the field of treatment and immunotherapy at
11 the time that they're reading that, which
12 could change over time.
13 Q. What was the understanding of the
14 term "immunotherapy" in 2015?
15 ATTORNEY RATLIFF: I object to the form
16 of the question, as well as to the premise of
17 the question.
18 A. So I think it would depend on the
19 context. I think as of -- if we're talking
20 about our critical date of July 10, 2015, you
21 know, a person of ordinary skill looking
22 through the MSI study record would already
23 understand that checkpoint blockade therapy
24 has been effective for a single patient with
25

metastatic colorectal cancer, who is MSI-high, would know that checkpoint blockade is FDA approved in other settings, such as melanoma, and would know that there is a lot of interest in testing that in MSI-high colon cancer, and would be very motivated to conduct the study described in the MSI study record and expect positive results.

Q. Does the term "immunotherapy" appear in Exhibit 1005?

A. I do not believe so.

ATTORNEY BROWN-MARSHALL: We can stop here for a break.

ATTORNEY RATLIFF: Okay.

THE WITNESS: Stop for lunch.

CERTIFIED STENOGRAPHER: Off the stenographic record at 12:17 p.m.

- - -

(Whereupon, a luncheon recess is taken at 12:17 p.m.)

* * * * * * * * *

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 A F T E R N O O N S E S S I O N
3 (1:01 p.m.)
4 CERTIFIED STENOGRAPHER: Back on the
5 stenographic record at 1:01 p.m.
6 BY ATTORNEY BROWN-MARSHALL:
7 Q. Welcome back, Dr. Oberstein.
8 A. Thank you.
9 Q. Dr. Oberstein, have you ever
10 participated in an investigator initiated
11 clinical trial?
12 A. Can you clarify what you mean by
13 that term?
14 Q. Well, are you familiar with the
15 term "investigator initiated clinical trial"?
16 A. So I have used the term before, but
17 I think there are many ways or multiple ways
18 to use the term.
19 Q. I see.
20 What is your understanding of what
21 the term means?
22 A. So, I mean, the words themself mean
23 that the investigator or one of the
24 investigators of the trial initiated that
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25 trial, but that could range from the

2 investigator coming up with an idea and then
3 another company sponsoring it and others
4 participating or them running the trial
5 completely on their own or something well in
6 between those two things.
7 Q. Have any of the clinical trials
8 that you've been participated in been
9 described as an investigator initiated
10 clinical trial?
11 A. So, yes.
12 Q. Okay. And were any of these
13 investigator initiated clinical trials related
14 to pembrolizumab?
15 A. Yes.
16 Q. And were you the principal
17 investigator on any of those investigator
18 initiated clinical trials that involved
19 pembrolizumab?
20 A. So for some of them, yes, for at
21 least a period of time.
22 Q. Okay. And did you design those
23 trials of pembrolizumab that were investigator
24 initiated clinical trials?
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. No, not all of them, but I have

designed a clinical trial that was investigator initiated utilizing pembrolizumab.

Q. Okay. And that investigator initiated clinical trial that you designed that involved pembrolizumab, was that sponsored by Merck?

A. So one of the trials that I was involved in was partially sponsored by Merck.

Q. Uh-huh.

A. And just to clarify, when I say it was an investigator initiated clinical trial, I was the principal investigator, but it was a team of investigators and scientists and representatives who designed the trial.

Q. Okay. Was Merck involved in the design of that investigator initiated clinical trial?

A. So Merck certainly had input and was involved in the design, yes.

Q. And did Merck provide funding for that investigator initiated clinical trial?

A. The trial I'm specifically thinking about, they provided funding for, yes.

2 Q. And did they provide funding at the
3 beginning of that investigator initiated
4 clinical trial?
5 A. They provided a commitment for
6 funding before the study opened.
7 Q. In your experience, how common are
8 investigator initiated clinical trials?
9 ATTORNEY RATLIFF: I object to the form
10 of the question.
11 A. I'm not sure what you mean by
12 "common."
13 Q. How frequently do they happen?
14 ATTORNEY RATLIFF: The same objection.
15 A. I can't report the frequency of
16 those trials.
17 Q. Uh-huh.
18 A. They're not uncommon, but I don't
19 know what percentages of trials are
20 investigator initiated.
21 Q. When it comes time for FDA approval
22 based on the clinical trial, do pharma
23 companies use the data that was acquired
24 during the investigator initiated clinical
25 trial?

1 ATTORNEY RATLIFF: I object to the form
2 of the question.
3 A. So I'm not very familiar with the
4 pharma companies' submissions to the FDA, on
5 what data they include in that.
6 Q. If you would turn to Paragraph 11
7 of your declaration.
8 And in Paragraph 11 you write:
9 Currently, I am the site principal
10 investigator on three active clinical studies
11 involving metastatic colorectal cancer
12 patients and two active clinical studies
13 involving PD-1 inhibitors, including
14 pembrolizumab.
15 Do you see that?
16 A. Yes.
17 Q. Okay. What three active clinical
18 studies are you involved in regarding
19 metastatic colorectal cancer?
20 A. So that might be an undercount, but
21 one of the trials I'm looking at is using the
22 medication called amivantamab and it is
23 evaluating the use in -- there is actually
24 three different trials that we're doing with
25

2 amivantamab looking at its use with metastatic
3 colorectal cancer.
4 Q. And I'm sure I'm going to butcher
5 this, amivantamab?
6 A. Amivantamab.
7 Q. Amivantamab, is that a monoclonal
8 antibody?
9 A. It is a bispecific antibody
10 essentially.
11 Q. And would you consider that an
12 immunotherapy?
13 A. No.
14 Q. No? Why not?
15 A. It doesn't target the immune
16 system.
17 Q. What about the second active
18 clinical study involving metastatic colorectal
19 cancer patients?
20 A. So actually just to clarify, I'm
21 working on three clinical trials in metastatic
22 colorectal cancer with amivantamab.
23 Q. Oh, okay. So all three are on --
24 A. But there are additional trials.

25 - - -

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 (Unintelligible, simultaneous
3 testimony interrupted by the certified
4 stenographer.)
5 - - -
6 CERTIFIED STENOGRAPHER: I need one at
7 a time, please.
8 A. So I am participating in three
9 active clinical trials utilizing amivantamab
10 in metastatic colorectal cancer. In addition,
11 I'm involved in other trials looking at
12 metastatic colorectal cancer, including a
13 clinical trial for medication called a KRAS
14 inhibitor, which is RMC9805. It's a small
15 molecule inhibitor of KRAS.
16 Q. Is that all of the clinical studies
17 that you're involved in that involve
18 metastatic colorectal cancer?
19 A. No. So I'm involved in additional
20 studies that I'm either not the principal
21 investigator or might be at some stages of
22 closing.
23 Q. And do any of those additional
24 studies involve using immunotherapies to treat
25 metastatic colorectal cancer?

A. So some of them do, yes.

Q. Okay. And which immunotherapies are those?

A. So one of the trials I was involved with, which is still open, but not accruing patients, was utilizing an agent called adenosine deaminase inhibitors, or CD73 antibodies, which are a component of the immune system, but not a checkpoint blockade.

Q. Any other immunotherapies for --

A. I'm also involved in a vaccine trial.

- - -

(Unintelligible, simultaneous testimony interrupted by the certified stenographer.)

- - -

CERTIFIED STENOGRAPHER: I need one at a time, please.

Q. Any other immunotherapies for clinical trials for metastatic colorectal cancer?

A. So I'm also involved in a cancer vaccine trial that's targeting metastatic

1 colorectal cancer. Again, it's not really an
2 active trial, it is completed, but we haven't
3 published the results yet, and we're still
4 monitoring patients.
5 Q. And does that vaccine trial in
6 metastatic colorectal cancer, does that
7 involve investigators from Johns Hopkins
8 University?
9 A. I don't believe so, but I can't be
10 certain about all the investigators.
11 Q. So, Dr. Oberstein, if you would
12 look at the last sentence in Paragraph 11, you
13 say: I have received more than $4.5 million
14 in funding in various pharmaceutical companies
15 related to my research activities.
16 Do you see that?
17 A. Yes, I do.
18 Q. And how do you use those
19 $4.5 million in funding for research
20 activities? What does that go to?
21 A. So let me just clarify where that
22 number comes from I think.
23 I don't actually keep track of
24 every budget for every clinical trial. We
25

1 have an office that does that.
2 Q. Uh-huh.
3 A. And all of that money goes to
4 support our clinical trial infrastructure and
5 running the clinical trials.
6 That number that we actually --
7 that I put down, 4.5 million, comes from a
8 federal website that collects information
9 about pharmaceutical sponsorship to
10 investigators for clinical trials that goes
11 back around five years, so that number is over
12 the last five years or so, maybe six, but most
13 recent years.
14 Q. Okay.
15 A. And to answer the question, that
16 money all goes to the university or the
17 hospital and they utilize it to fund and
18 operate the trials.
19 Q. And did some of that $4.5 million
20 in funding come from Merck?
21 A. I would suspect so over the last
22 six years, yes.
23 Q. Okay. And approximately what
24 percentage of that $4.5 million came from
25

1 Merck?
2 A. I can't answer that. I'm not sure.
3 ATTORNEY BROWN-MARSHALL: I'd like to
4 mark this as Exhibit 2408. Oh, 2407.
5 - - -
6 (Whereupon, document entitled Paul
7 E. Oberstein | OpenPayments, is received and
8 marked as Exhibit 2407 for Identification.)
9 - - -
10 CERTIFIED STENOGRAPHER: Number 2407.
11 BY ATTORNEY BROWN-MARSHALL:
12 Q. And, Dr. Oberstein, are you
13 familiar with this document?
14 ATTORNEY RATLIFF: And I object to
15 Exhibit 2407 for purposes of authentication,
16 foundation, and hearsay.
17 A. I've never seen this printing of it
18 before, but I'm familiar with the website
19 OpenPaymentsData.cms.gov.
20 Q. Okay. And is that the website that
21 you were mentioning about a government website
22 that keeps track of funding for research and
23 other purposes that physicians receive?
24 A. Yes.
25

1 Q. Okay. And this is the entry from
2 OpenPaymentsData.cms.gov related to you;
3 correct?
4 A. Correct.
5 Q. Okay. If you'd turn to the second
6 page, there is a chart in the middle, and you
7 see that according to this website, you
8 received approximately $4.5 million in
9 associated research funding; is that correct?
10 A. That is correct, and like I said
11 before, that money doesn't go to me. It goes
12 to the university that operates the clinical
13 trials.
14 Q. Okay. And then you see at the top
15 of that chart, there is an entry for general
16 payment record.
17 Do you see that?
18 A. Yes.
19 Q. Okay. What are general payments?
20 A. So generally, general payments I
21 think refer to either consulting compensation
22 or fees for travel or other compensation to
23 support an individual.
24 Q. And according to this website, you
25

received $125,000 in general payments; correct?

A. Correct.

Q. Okay.

If you would turn to Page 30 -- or actually, let's start at the bottom of Page 2.

Do you see the headline: Top Companies Making Associated Research Funding?

Do you see that?

A. Yes.

Q. Okay. And if you'd turn to the next page, there is a chart that follows that heading, okay? And according to this chart, the top contributors to your research funding is Merck; correct?

A. That's what it says in the chart, yes.

Q. And according to the chart, you've received approximately $2.4 million in research funding from Merck; is that correct?

A. So just to clarify, this is funding that goes to my university from Merck, but yes, it does accurately reflect that.

Q. And Merck is by far the largest

2 contributor to your research; correct?

3 A. So I don't think that's accurate,

4 but on this chart that's what's reported.

5 Q. Okay. So you don't think that the

6 government payment system has the correct --

7 let me finish my question, has the correct

8 monetary value for contributions to your

9 research?

10 ATTORNEY RATLIFF: I object to the form

11 of the question, as well as to the premise of

12 the question.

13 A. So I think that there is not

14 standardization about how these payments are

15 reported, and I don't -- and it's

16 self-reported by companies, not by the

17 government. So I don't think it reflects the

18 entirety of the research payments that I've

19 received or have been received for trials that

20 I was affiliated with over this time period.

21 Q. But do you question the fact that

22 you've received over $2.25 million in funding

23 from Merck?

24 A. I do not question that.

THE SULLIVAN GROUP OF COURT REPORTERS

25 Q. So when you receive research

2 funding from Merck, are those funds provided
3 under some sort of agreement?
4 A. What do you mean by that?
5 Q. Do you have an agreement with Merck
6 that governs the payment of research funding
7 that you've received from Merck?
8 A. You mean me, personally, or the
9 institution that I work for?
10 Q. Either one?
11 A. So I don't personally receive any
12 research funding from Merck. None of this
13 money goes to me and none of it is an
14 agreement that I have. The institution that I
15 work for, either Columbia, which is where a
16 lot of this came to, or NYU have research
17 agreements, clinical trial agreements with
18 pharmaceutical companies.
19 Q. Including Merck?
20 A. Including Merck.
21 Q. Do you or your university keep
22 records of payments that are received from
23 Merck in relation to clinical trial research?
24 A. I do not keep record of those
25 payments. I can't speak for my university.

2 Q. Aside from research funding, do you
3 have any other relationships with Merck?
4 A. What do you mean by
5 "relationships"?
6 Q. Do you serve on any advisory boards
7 for Merck?
8 A. So in the past, I served on
9 advisory board for Merck. I don't think I
10 actually am currently, but it's sometimes hard
11 to know if it's a one-time thing, whether it
12 will happen again.
13 Q. And what was that advisory board
14 related to?
15 A. So in I think 2017 to around 2020,
16 I was on a gastric cancer advisory board for
17 Merck.
18 Q. And did that involve pembrolizumab
19 or Keytruda?
20 A. I mean, it was for Merck. It
21 involved anything that Merck wanted to discuss
22 with the advisory board for gastric cancer.
23 Q. Have you been a sponsored speaker
24 on behalf of Merck?
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. I don't recall that, but I can't

2 recall every single speakership I've done.
3 Q. Have you received any travel funds
4 from Merck?
5 A. So certainly associated with the
6 advisory board that I was on, there would have
7 been travel funds that went along with that.
8 Q. Have you received travel funds from
9 Merck related to any other purpose?
10 A. Such as?
11 Q. Speaking at a conference?
12 A. I don't think so.
13 Q. Have you received any honoraria
14 from Merck?
15 A. Outside of the context of being on
16 an advisory board?
17 Q. Yes.
18 A. I don't think I've received
19 anything outside of our advisory board
20 agreements.
21 Q. And did you receive an honoraria as
22 part of being on the advisory board?
23 A. So generally, you're compensated
24 for being part of an advisory board, either on

25 a standing basis or on an ad hoc basis.

Q. If you would turn to Paragraph 16 in your declaration.

You can put this aside.

So Paragraph 16 you wrote: I have published more than 30 peer-reviewed papers and have presented more than 25 oral and poster presentations regarding GI cancers, including the use of checkpoint inhibitors to treat GI cancers. Is that correct?

A. That is correct.

Q. How many of those 30 peer-reviewed publications were first authored papers?

A. I don't recall that offhand. I don't have that information offhand, but it's included in the CV that I attached to this document.

Q. Can you ballpark how many?

A. I wouldn't be comfortable doing that. I'd like to see the CV.

Q. Have you ever published in the New England Journal of Medicine?

A. I have not.

Q. Have you ever published in Science?

THE SULLIVAN GROUP OF COURT REPORTERS

A. I have not.

Q. Have you ever published in the Journal of the American Medical Association?

A. I don't think so.

Q. Have you ever published in the journal Cell?

A. I have not.

Q. Have you ever published in Lancet?

A. I'm not sure.

Q. And we were looking at one of your publications earlier or one of your coauthors was Dr. Dung Le; correct?

A. That is correct.

Q. Okay. And what is your opinion of Dr. Le's research?

ATTORNEY RATLIFF: I object to the form of the question.

A. I don't think I could answer that question. I'm not sure what you mean by "opinion" and how you encompass all someone's research.

Q. Are you familiar with Dr. Le's reputation in the oncology community?

A. I don't think I could report on her general reputation, no.

Q. What is your perception of her reputation?

A. I really feel it's well beyond the scope of something. I don't generally opine on other people's reputation and have not given that thought.

Q. So you don't have an opinion on Dr. Le's reputation?

A. Reputation for what?

Q. So her research reputation?

A. I don't have an opinion.

Q. Okay. And have you worked with any of the other inventors on the '393 patent? I'll give them to you one at a time. Dr. Luis Diaz?

A. I do not believe so.

Q. Have you ever worked with Dr. Bert Vogelstein?

A. I do not believe so.

Q. Okay. Have you ever worked with Dr. Ken Kinzler?

A. I do not believe so.

Q. Okay. Have you ever worked with Dr. Nickolas Papadopolous?

A. So I give the same answer though, it does depend on what you mean by work with. We have discussed research ideas together before.

Q. Okay. Which of those folks have you discussed research --

A. Sorry. I specifically recall Dr. Papadopolous coming to present some of his research to me and my team and discussing a collaboration, but we never went beyond that stage.

Q. Have you ever worked with Dr. Drew Pardoll?

A. I have not.

Q. Have you ever worked with Dr. Suzanne Topalian?

A. I have not.

Q. Okay. You mentioned you have 25 oral and poster presentations; is that correct?

A. I think more than that number, but that, at least that number, yes.

Q. And were any of those oral or poster presentations made at the ASCO

1 conference?
2 A. Yes.
3 Q. And were any of those presentations
4 late-breaking presentations?
5 A. I don't recall right now.
6 Q. Do you usually attend ASCO?
7 A. What do you mean by "usually"?
8 Q. How often do you attend ASCO?
9 A. Most years I attend ASCO, unless
10 there is some reason why I can't or it gets
11 canceled.
12 Q. And did you attend Dr. Le's
13 presentation at the 2015 ASCO conference?
14 A. So I don't have any specific
15 recollection of attending that presentation.
16 Q. So, Dr. Oberstein, looking back to
17 your declaration, in your declaration, you
18 don't provide any opinions on anticipation; is
19 that correct?
20 ATTORNEY RATLIFF: I object to the form
21 of the question, as well as to the premise of
22 the question.
23 A. So in my declaration, I was asked
24 to serve as an expert consultant for the '393
25

1 patent from the perspective of person of
2 ordinary skill as of July 10, 2015, and I did
3 that. And I think applying that perspective,
4 I found and noted that all the claims of the
5 '393 patent were taught or suggested by the
6 MSI-high study record alone and with various
7 prior art references.
8 Q. So you provide the opinion that
9 they were taught or suggested, but you don't
10 provide an opinion that they were anticipated?
11 ATTORNEY RATLIFF: I object to the form
12 of the question, as well as to the premise of
13 the question.
14 A. So I did not say that. I found
15 that all of the -- each and every claim
16 limitation in the '393 patent was taught in
17 the MSI-high study record and with various
18 prior art references.
19 Q. But you don't provide an opinion
20 that those claims were anticipated by the
21 MSI-high study record?
22 ATTORNEY RATLIFF: I object to the form
23 of the question, as well as to the premise of
24 the question.

A. So I did not say that. I found that each and every claim limitation of the '393 patent was taught in the MSI-high study record from the perspective of a person of ordinary skill in the art as of July 10, 2015.

Q. And you don't provide any opinion that the claims of the '393 patent were rendered obvious; correct?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. So I'll restate my primary finding, which is that each and every claim limitation of the '393 patent was taught in the prior art references, including the MSI-high study record as of July 10, 2015, for a person of ordinary skill in the art.

Q. But you don't use the word "obviousness"?

A. I would just restate my primary finding, which is that each and every claim of the '393 patent was taught in the prior art, including the MSI study record for a person of ordinary skill as of July 10, 2015.

2 Q. And what you're calling your
3 primary finding does not contain the word
4 "obviousness"; correct?
5 A. So I'll say it again. I think that
6 it's my opinion that each and every claim
7 limitation of the '393 patent is taught in the
8 MSI-high study record alone and in combination
9 with prior art references for a person of
10 ordinary skill in the art as of July 10, 2015.
11 Q. And when you said that, you did not
12 use the word "obvious"; correct?
13 A. Correct.
14 Q. And in your declaration, you do not
15 provide opinions on nexus; is that correct?
16 ATTORNEY RATLIFF: I object to the form
17 of the question, as well as to the premise of
18 the question.
19 A. So in my declaration, I provide in
20 .12 a discussion about secondary
21 considerations alleged by JHU and find that
22 they were fundamentally flawed, as I detailed,
23 because many of them refer to publications
24 that were not evaluated at the critical date
25 of July 10, 2015, and thus I think they're

2 flawed in their presentation.
3 Q. But as part of your analysis in
4 .12, you did not provide a nexus analysis;
5 correct?
6 ATTORNEY RATLIFF: I object to the form
7 of the question, as well as to the premise of
8 the question.
9 A. So my analysis in .12 is that the
10 secondary considerations are flawed and that
11 they are not applicable as of the critical
12 date of July 10, 2015.
13 Q. And your .12 does not use the word
14 "nexus"; correct?
15 A. My finding in .12 is that the
16 secondary considerations are fundamentally
17 flawed as of the date of July 10, 2015, and
18 thus don't form the basis for further
19 argument.
20 Q. And that does not contain the word
21 "nexus"; correct?
22 A. Correct.
23 Q. So if you look at Header Number 7
24 in your table of contents, you say: The

25 claims of the '393 patent are taught or

1 suggested by the prior art.
2 What does it mean for the prior art
3 to teach or suggest the claims of the '393
4 patent?
5 A. I'm not sure I understand the
6 question.
7 Q. Well, you wrote the words: The
8 claims of the '393 patent are taught or
9 suggested by the prior art; correct?
10 A. I did write those words, yes.
11 Q. Okay. What does it mean for the
12 claims of the '393 patent to be taught or
13 suggested by the prior art?
14 A. It means that the prior art
15 contains the claims of the '393 patent from
16 the perspective of a person of ordinary skill
17 evaluating the prior art on July 10, 2015.
18 Q. What's the difference between
19 teaching and suggesting?
20 A. So some -- I would say teaching
21 refers to things that are said explicitly and
22 suggestion are things that are implicit.
23 Q. And how did you assess whether the
24 prior art taught claims of the '393 patent?
25

2 A. I'm sorry, can you repeat that?
3 Q. How did you assess whether the
4 prior art taught the claims of the '393
5 patent?
6 A. I utilized a perspective of a
7 person of ordinary skill and the available
8 prior art as of July 10, 2015, analyzed the
9 claims in the '393 patent and then determined
10 or looked to see whether they were taught in
11 the prior art.
12 Q. How did you assess whether the
13 prior art suggested the claims of the '393
14 patent?
15 A. So in the same way I looked at the
16 claims in the '393 patent and what was
17 reported in the prior art as of July 10, 2015,
18 and using the perspective of a person of
19 ordinary skill, determined what would be
20 suggested by what was written in the prior
21 art.
22 Q. In your declaration, do you provide
23 an opinion on reasonable expectation of
24 success?
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. Sorry. Could you repeat the

1 question?
2 Q. In your declaration, do you provide
3 an opinion on reasonable expectation of
4 success?
5 A. I'm sorry, what do you mean by "an
6 opinion on reasonable expectation of success"?
7 Q. So maybe it will help to look at an
8 example. Can you go to Page 68 of 102.
9 A. Yes, I'm there.
10 Q. Okay. Oh, I'm sorry, Page 59 of
11 102.
12 A. Yes.
13 Q. And you see at the very bottom and
14 continuing onto the next page it says:
15 Additional Dr. Neugut explains that the state
16 of the art known to the POSA as of July 10,
17 2015 --
18 A. I'm sorry, I don't think I have the
19 right page.
20 I've got it now. Thank you.
21 Q. Got it.
22 July 10, 2015, would counsel the
23 POSA to carry out the methods of treatment
24 found in the MSI-high study record with a
25

2 reasonable expectation of success.
3 Do you see that?
4 A. I do see that, yes.
5 Q. Okay. So you're providing opinions
6 on reasonable expectation of success?
7 A. So I'm providing an opinion that a
8 POSA would be motivated to carry out the
9 clinical trial described in the MSI-high study
10 record with a reasonable expectation of
11 success.
12 Q. And you agree with Dr. Neugut on
13 that point; correct?
14 A. I'm not sure what you mean by that.
15 Q. So you say that Dr. Neugut explains
16 the state of the art known to a POSA as of
17 July 10 would counsel the POSA to carry out
18 the methods of treatment found in the MSI-high
19 study record with a reasonable expectation of
20 success.
21 Do you agree with that statement?
22 A. So, yes, I agree with Dr. Neugut,
23 that the state of the art at the relevant time
24 of July 10, 2015 would motivate a POSA to

25 carry out the methods of treatment found in

1 the study record with a reasonable expectation
2 of success, because as I state, the POSA would
3 have known that physicians had successfully
4 treated a colorectal cancer patient who was
5 MSI-high with a PD-1 inhibitor with a complete
6 response and that pembrolizumab was approved
7 for another oncology indication prior to that
8 date.
9 Q. Did you apply the same standard for
10 reasonable expectation of success that
11 Dr. Neugut applied?
12 A. I don't know what Dr. Neugut's
13 reasonable expectation of success standard is,
14 but I utilized my standard in independently
15 evaluating what a POSA would have done at that
16 time.
17 Q. Okay. And what was your standard
18 that you apply for reasonable expectation of
19 success?
20 A. So the standard I utilized is
21 whether a person of ordinary skill, who was
22 familiar with the prior art and knew about
23 success of treating MSI-high colon cancer in
24 one patient and the success of pembrolizumab

2 in other cancers, would be motivated to treat
3 a patient according to the method described in
4 the MSI study record and expect that that
5 would provide benefit for the patient over not
6 doing that.
7 Q. When you say "treat a patient
8 according to the method described in the
9 MSI-high study record," is that patient
10 MSI-high or not?
11 A. So in my previous example, as I
12 stated, I think a POSA would have been
13 motivated to treat an MSI-high colorectal
14 cancer patient with the method described in
15 the MSI-high study record based on the
16 knowledge at that time that a previous patient
17 with MSI-high colon cancer had a complete
18 response and that pembrolizumab is approved
19 for other immunotherapy indications in cancer
20 with a reasonable expectation of success for
21 that patient.
22 Q. All right.
23 Dr. Oberstein, if you would turn to
24 Paragraph 21 in your declaration.
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25 And in Paragraph 21 you write: I

1 understand that JHU argues that the term "in
2 response to" should be construed to mean in
3 reaction to; correct?
4 A. That's correct.
5 Q. Okay. And you write further: I
6 understand that the parties do not dispute
7 that the term "in response to" requires
8 causality; correct?
9 A. That's correct.
10 Q. Okay. Is Merck -- strike that.
11 Are you offering a construction of
12 the term "in response to"?
13 A. That's different than what I write.
14 Q. Let's try it this way: What
15 meaning of "in response to" did you apply in
16 forming your opinions?
17 A. So as I wrote there, I understand
18 that the parties do not dispute that the term
19 "in response to" requires causality and that's
20 what I utilized.
21 Q. So you are not using a construction
22 of the term "in response to"; correct?
23 ATTORNEY RATLIFF: I object to the form
24 of the question.
25

A. I'm not sure what you mean by "construction."

Q. Are you applying the plain meaning of "in response to"?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. I don't know what you mean by "plain meaning." I understand that the parties do not dispute that the term "in response to" requires causality and that's what I utilized.

Q. Okay. So you used the term "in response to" with those words, with the addition that it requires causality; is that correct?

ATTORNEY RATLIFF: I object to the form of the question.

A. That's correct.

Q. Okay. So in forming your opinions in your declaration, you did not use -- you did not interpret "in response to" to mean after; correct?

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A. So as I stated here, I went with

2 what I understand to be the opinion of both
3 parties that the term "in response to"
4 requires causality.
5 Q. Okay. So in forming your opinions,
6 how did you assess causality with respect to
7 the term "in response to"?
8 A. I'm sorry, I don't understand the
9 question.
10 Q. So you said that you interpreted
11 "in response to" as meaning in response to
12 with a requirement that there be causality;
13 correct?
14 A. Correct.
15 Q. Okay. How did you determine that
16 there was causality with respect to the term
17 "in response to"?
18 ATTORNEY RATLIFF: It's the same
19 question. I object to the form of the
20 question.
21 A. I still am not sure if you mean in
22 the study record, in the patent, in the --
23 Q. What does it mean that "in response
24 to" requires causality?

25 A. It means that the action is taken

2 in response to the first finding.
3 Q. How did you determine that a given
4 action was taken in response to with
5 causality?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. So I don't understand the question,
9 but let me go back to my finding, which is
10 that in the ClinicalTrials.gov study record,
11 which was available to a person of ordinary
12 skill as of July 10, 2015, there is a cohort
13 of patients who are required to be enrolled
14 with MSI positive colorectal cancer.
15 Q. Uh-huh.
16 A. So I think a person of ordinary
17 skill reading that requirement would
18 understand that in order to be enrolled in
19 this study and receive treatment in that arm,
20 a subject would have to have MSI-high
21 colorectal cancer and then be treated with an
22 effective dose of pembrolizumab after
23 determining that fact.
24 Q. So the evidence of causality that

25 you're relying on is the fact that Arm 1

1 described in what you call the MSI-high study
2 record includes only MSI-high colorectal
3 cancer patients?
4 ATTORNEY RATLIFF: I object to the form
5 of the question, as well as to the premise of
6 the question.
7 A. So I'm stating that in the MSI
8 study record, MSI-high study record, Arm 1
9 describes treating a patient who is MSI
10 positive colorectal cancer with an effective
11 dose of pembrolizumab based on their
12 qualification in that arm as having MSI
13 positive colorectal cancer.
14 Q. So the fact that the patients in
15 Arm 1 were all MSI-high colorectal cancer
16 patients indicates to you that there was
17 causality with treating those patients with
18 pembrolizumab in response to determining that
19 they are MSI-high?
20 ATTORNEY RATLIFF: I object to the form
21 of the question.
22 A. So the fact that that is an
23 inclusion criteria and required in order for a
24 patient to be treated on a trial in that arm
25

2 means that they have to have that
3 qualification in order to be treated on the
4 trial.
5 Q. And you don't rely on any other
6 evidence in the MSI-high study record to
7 indicate the causality associated with
8 treating in response to determining the
9 patient is MSI-high?
10 ATTORNEY RATLIFF: I object to the form
11 of the question, as well as to the premise of
12 the question.
13 A. So I rely on the information, which
14 I just described to you, which I think is
15 sufficient to indicate causality in Arm 1 for
16 patients with MSI-high colorectal cancer being
17 treated with an effective dose of
18 pembrolizumab in response to being MSI-high.
19 Q. Did Merck inform you that they have
20 previously argued that "in response to" means
21 "as the reaction specifically to"?
22 ATTORNEY RATLIFF: I object to the form
23 of the question, as well as to the premise of
24 the question.
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. Sorry. Can you repeat the

1 question?
2 Q. Did Merck inform you that they have
3 previously argued that "in response to" means
4 "as the reaction specifically to"?
5 ATTORNEY RATLIFF: I object to the form
6 of the question, as well as to the premise of
7 the question.
8 A. So I'm not sure if you're
9 suggesting that's different than what I wrote
10 here, which is that the parties do not dispute
11 that the term "in response to" requires
12 causality. That is what I was communicated by
13 Merck. That's what I put in my declaration.
14 Q. So your construction or the meaning
15 that you utilize for "in response to" is
16 consistent with "as the reaction specifically
17 to"?
18 A. Again, I'm not sure what you're
19 trying to clear with those words. Is that
20 different than causality? That's what I used.
21 Q. You tell me.
22 A. So I understand that the parties do
23 not dispute that the term "in response to"
24 requires causality, and that is what I adopted
25

2 and included in my opinion.

3 Q. If you had used the construction

4 "as the reaction specifically to," would that

5 change your opinion?

6 ATTORNEY RATLIFF: I object to the form

7 of the question.

8 A. I am not sure. I have to

9 reconsider. In that light, that's not what I

10 used.

11 Q. That's not what you used. Okay.

12 If you would, let's go to

13 Paragraph 23. And you say: I understand the

14 POSA for purposes of my analysis of the '393

15 patent is an oncologist or a medical

16 professional in a related field with at least

17 five years of experience with treating cancer

18 patients; correct?

19 A. That's correct.

20 Q. Okay. And what is the source of

21 that understanding of a definition of a POSA?

22 A. You're asking me where did I get

23 that definition from?

24 Q. Uh-huh.

THE SULLIVAN GROUP OF COURT REPORTERS

25 A. So I saw that definition in

1 Dr. Neugut's declaration, and then I was
2 advised by my counsel to utilize that
3 definition in preparing my assessment.
4 Q. Okay. What do you mean by a
5 medical professional in a related field?
6 A. So not only oncologists. There are
7 other people who can treat cancer patients,
8 like nurse practitioners or related radiation
9 oncologist who I think would be appropriate as
10 a POSA.
11 Q. So you think a nurse practitioner
12 would qualify as a POSA under Merck's
13 definition?
14 A. It depends on who they were and if
15 they are a medical professional treating
16 cancer patients.
17 Q. Okay. In Paragraph 24 you write:
18 I disagree with JHU's definition for the POSA
19 given that the '393 patent relates to cancer
20 therapy and provides a method of treating a
21 cancer patient; is that correct?
22 A. That is correct.
23 Q. Okay. So you also assessed JHU's
24 definition of the POSA; correct?
25

2 A. By "assess," do you mean did I
3 review it?
4 Q. Well, you disagree with their
5 definition; correct?
6 A. Correct.
7 Q. So you must have determined that
8 there is something wrong with their
9 definition?
10 A. Correct.
11 Q. Okay. And how did you assess JHU's
12 definition of a POSA?
13 A. Again, I'm not sure I understand.
14 What method did I use to assess it?
15 Q. Are there certain requirements of a
16 POSA that you feel like JHU's definition did
17 not meet?
18 A. So, as I stated here, I disagree
19 with JHU's definition for the POSA because the
20 patent is essentially a cancer therapy patent,
21 so it's a method to give a cancer therapy to
22 patients and it provides a method of treating
23 an actual cancer patient, which is why I think
24 it's not correct to involve someone as a POSA

25 who doesn't have an active role in treating

1 cancer patients and providing this therapy to
2 patients.
3 Q. So in your understanding, a POSA is
4 someone who is actively using the method of a
5 claim?
6 ATTORNEY RATLIFF: I object to the form
7 of the question, as well as to the premise of
8 the question.
9 A. I think a POSA is a person who
10 would be able to appreciate the aspects of the
11 claim and that will be able to assess them.
12 Q. And where did that understanding
13 come from?
14 A. That is the understanding that I
15 think I received from my counsel, but I can't
16 say exactly.
17 Q. And in your opinion, someone who
18 understands the steps of a claimed method of
19 treatment would qualify as a POSA; correct?
20 ATTORNEY RATLIFF: I object to the form
21 of the question.
22 A. Could you repeat the question?
23 Sorry?
24 Q. So in your opinion, someone who
25

2 understands the steps of a claimed method of
3 treatment would qualify as a POSA?
4 ATTORNEY RATLIFF: I object to the form
5 of the question, as well as to the premise of
6 the question.
7 A. So I don't think understanding the
8 steps alone would qualify a person as a POSA.
9 They'd also have to have some knowledge and
10 experience in applying the methods described
11 in the claims.
12 Q. Uh-huh.
13 A. In this case, a method of providing
14 cancer therapy and treating a cancer patient.
15 Q. Did you determine whether Merck's
16 definition of the POSA would exclude any of
17 the inventors on the '393 patent?
18 A. I did not determine that.
19 Q. Okay. Why not?
20 A. I don't think that was relevant to
21 my assessment and analysis here.
22 Q. Okay. So the inventors on a patent
23 are not relevant to the assessment of a person
24 of ordinary skill with respect to that patent?

25 ATTORNEY RATLIFF: I object to the form

of the question, as well as to the premise of the question.

A. I'm sorry, what connection are you making between the inventors and the POSA?

Q. So I'm just saying -- so in your opinion, looking at the inventors on a patent is not relevant to the assessment of who the person of ordinary skill would be on that patent?

ATTORNEY RATLIFF: Is that a statement you're just saying? Or is that a question?

A. Is that a question?

Q. Yes.

In your opinion, looking at the inventors on a patent is not relevant to the assessment of who the person of ordinary skill would be on that patent?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I don't think that a person of ordinary skill for the purposes of evaluating a patent needs to be an inventor of the patent, if that's what you're asking, because they're not identical roles.

2 Q. So it's okay for the definition of
3 a person of ordinary skill to exclude some
4 inventors in your opinion?
5 ATTORNEY RATLIFF: And the inventors
6 you're talking about are inventors that are
7 corrected on the patent or --
8 ATTORNEY BROWN-MARSHALL: Counsel,
9 that's enough with the speaking objections.
10 I'll ask the questions --
11 ATTORNEY RATLIFF: That wasn't an
12 objection. It's a clarification to your
13 question.
14 ATTORNEY BROWN-MARSHALL: That is a
15 speaking objection.
16 ATTORNEY RATLIFF: It's not an
17 objection. If you don't want to respond to my
18 question, then I object to the form of your
19 question.
20 A. So I don't think it's irrelevant,
21 but I don't think that a person in order to be
22 defined as a POSA has to be suitable to be the
23 inventor of the patent.
24 BY ATTORNEY BROWN-MARSHALL:
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25 Q. And I'm not asking whether they're

2 suitable. I'm saying if your definition of a
3 POSA excludes inventors, is that an acceptable
4 definition of a POSA?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. So I'm not sure.
8 Q. Okay. And in Paragraph 25 you say:
9 All of my opinions expressed in this
10 declaration are from this perspective of the
11 POSA as of the critical date of the '393
12 patent.
13 What do you mean by "this
14 perspective of the POSA"?
15 A. So I defined in Paragraph 23 that I
16 understand the POSA is an oncologist or a
17 medical professional in a related field with
18 at least five years of experience treating
19 cancer patients.
20 The POSA would also have experience
21 in or access to a person with knowledge of
22 clinical trials for therapeutics and how they
23 work, as well as experience with or access to
24 a pathologist with comparable experience.
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25 Q. Dr. Oberstein, if you would turn to

1 Exhibit 1005. I believe you have a copy in
2 front of you.
3 ATTORNEY BROWN-MARSHALL: Mark this as
4 Exhibit 1005.
5 - - -
6 (Whereupon, document MERCK EX1005,
7 is received and marked as Exhibit 1005 for
8 Identification.)
9 - - -
10 CERTIFIED STENOGRAPHER: Number 1005.
11 BY ATTORNEY BROWN-MARSHALL:
12 Q. And, Dr. Oberstein, we've talked
13 about this exhibit previously. This is the
14 June 10, 2013 submission to
15 ClinicalTrials.gov; correct?
16 ATTORNEY RATLIFF: I object to the form
17 of the question.
18 A. That is correct.
19 Q. And this ClinicalTrials.gov
20 submission is related to the Clinical Trial
21 Number NCT01876511; correct?
22 A. That is correct.
23 Q. And did you participate in that
24 clinical trial?
25

2 A. No, I did not.
3 Q. So you didn't have any patients
4 enrolled in that study?
5 A. No, I did not.
6 Q. And if you look starting on Page 1
7 and continuing on to Page 2, there is a list
8 of 28 submissions to ClinicalTrials.gov;
9 correct?
10 A. That is correct.
11 Q. And it's your understanding that
12 all 28 of those submissions are related to
13 Clinical Trial Number NCT01876511?
14 A. I would assume that, but I have not
15 reviewed all 28 of those submissions.
16 Q. Okay. How many of those
17 submissions did you review?
18 A. I don't recall. I definitely
19 reviewed more than one, but I don't recall if
20 I reviewed more than two or three.
21 Q. Okay. And which additional two or
22 three submissions did you review?
23 A. So I recall reviewing probably the
24 one dated June 9, 2015, or Version 11 because

25 that was the one that was closest to the

2 critical date of the patent of July 10, 2015.
3 Q. Uh-huh.
4 A. I don't recall if I looked at other
5 ones as well.
6 Q. Okay. But you don't rely on that
7 June 9, 2015 submission in your declaration;
8 correct?
9 A. That is correct. I rely on the one
10 in front of us.
11 Q. If you would turn to Page 5 of the
12 exhibit. And you see about two-thirds of the
13 way down under eligibility there is a
14 category: Criteria, inclusion criteria.
15 Do you see that?
16 A. Yes, I see that.
17 Q. Okay. What is the purpose of
18 inclusion criteria in a clinical trial?
19 A. As the name implies, inclusion
20 criteria is something that is necessary to be
21 accurate to be included in the clinical trial.
22 Q. And looking at the inclusion
23 criteria in this exhibit, nothing in those
24 inclusion criteria requires that the patients

25 have a certain stage of cancer; correct?

1 ATTORNEY RATLIFF: I object to the form
2 of the question.
3 A. So I don't think anything in the
4 inclusion criteria says about the stage of
5 cancer, but a person of ordinary skill in the
6 art would understand that if a patient is
7 going on a clinical trial, it would only be
8 appropriate at that time when they're
9 evaluating this clinical trial record to be a
10 person who has metastatic or incurable
11 colorectal cancer and has already progressed
12 on one or two lines of therapy, specifically
13 two lines if possible, before it would be
14 appropriate to go on a clinical trial as
15 recommended in ClinicalTrials.gov.
16 Q. So it's your opinion that there are
17 additional inclusion criteria that are
18 unstated in this MSI -- what you called the
19 MSI-high studied record?
20 ATTORNEY RATLIFF: I object to the form
21 of the question.
22 A. So I'm not sure what you mean by
23 "inclusion criteria." I think that a person
24 of ordinary skill reading this study record
25

1 would understand a certain thing about the MSI
2 positive colorectal cancer and would
3 understand that it's only appropriate for that
4 person to go on a trial if they have
5 metastatic disease and have progressed in
6 prior therapy.
7 Q. The people reading these
8 submissions on ClinicalTrials.gov, they're not
9 limited to what you define as a person of
10 ordinary skill in the art; correct?
11 A. That is correct. This is an open
12 document. Anyone can read it.
13 Q. Okay. So for a colorectal cancer
14 patient reading the MSI-high study record,
15 they're going to look at these inclusion
16 criteria and they're going to think, Well, it
17 doesn't say that I have to be Stage 4, I'm
18 Stage 2, I could potentially enroll; correct?
19 A. Is that a question?
20 ATTORNEY RATLIFF: I object. It sounds
21 like it is a question. I object to the form
22 of the question, if it is a question.
23 A. So I don't really know what a
24 patient or someone else looking at this would
25

2 say. I evaluated this and reported on this
3 from the perspective of a person of ordinary
4 skill in the art as of July 10, 2015, and at
5 that time, a POSA would have looked at this
6 and said, If this clinical trial is being
7 tested in MSI positive colorectal cancer,
8 that's referring to a patient who has advanced
9 disease and has failed prior therapy.
10 Q. Even though that's not explicitly
11 stated in the inclusion criteria?
12 ATTORNEY RATLIFF: Hold on.
13 I object to the form of the question,
14 as well as to the premise of the question.
15 A. I think that would be obvious to a
16 POSA looking at this document.
17 Q. And there is nothing in the
18 inclusion criteria that explicitly requires
19 prior therapy; correct?
20 A. As I just stated, there is nothing
21 that explicitly says one or two prior
22 therapies are needed, but a POSA looking at a
23 study of a novel therapy in MSI positive
24 colorectal cancer would understand and know
25 that this person has to have advanced

1 incurable disease and have progressed from
2 prior therapy.
3 Q. In your clinical trials that you've
4 conducted, if prior therapy is required for a
5 patient to enroll, have you explicitly stated
6 that in the inclusion criteria?
7 A. I don't recall specifically. I'd
8 have to look at those references to answer
9 that.
10 Q. Have you -- in the clinical trials
11 that you have designed, have you ever assumed
12 that doctors would understand what your
13 inclusion criteria are even if you don't list
14 them?
15 A. I've used different standards I
16 would say in submitting information, but
17 absolutely understand that someone else
18 reading this has to have some knowledge in
19 order to interpret it, in light of what
20 they're going to be using it for, and it would
21 be very customary to rely on an outside expert
22 or, sorry, an outside POSA to evaluate what
23 I'm writing in ClinicalTrials.gov posting.
24 Q. Can you identify any clinical trial
25

1 that you've conducted in which metastatic
2 cancer was a requirement in which you haven't
3 explicitly written that in the inclusion
4 criteria?
5 ATTORNEY RATLIFF: I object to the form
6 of the question.
7 A. You mean the inclusion criteria on
8 ClinicalTrials.gov
9 Q. Yes.
10 A. So I've not reviewed my postings
11 and I can't tell you whether that has occurred
12 or not occurred.
13 Q. Would you be comfortable with a
14 ClinicalTrials.gov submission for a clinical
15 trial that required patients that have
16 metastatic cancer, but does not specifically
17 include metastatic cancer in the inclusion
18 criteria?
19 ATTORNEY RATLIFF: I object to the form
20 of the question.
21 A. What do you mean by "comfortable"?
22 Q. Well, you previously testified that
23 you review and sign off on the
24 ClinicalTrials.gov submissions for your
25

2 clinical trials; correct?
3 A. That is correct.
4 Q. Okay. If you were conducting a
5 clinical trial in which metastatic cancer was
6 required for enrollment, would you be
7 comfortable signing off on the
8 ClinicalTrials.gov submission that did not
9 list metastatic cancer in the inclusion
10 criteria?
11 ATTORNEY RATLIFF: I object to the form
12 of the question.
13 A. So it's a theoretical question and
14 I'm not 100 percent sure what I would do in
15 the real moment, but I would be very confident
16 that anyone with experience treating
17 colorectal cancer patients, who is interested
18 in putting a patient on the trial, learning
19 about the trial, would understand from this
20 description that this is relevant for a
21 patient with advanced cancer who has failed
22 prior chemotherapy.
23 ATTORNEY RATLIFF: And I'll just note
24 for the record that when Dr. Oberstein said
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25 "this description," he was pointing with his

1 fingers to Exhibit 1005.
2 Q. Is it your opinion that if a
3 colorectal cancer patient who was not
4 metastatic would be excluded from this
5 clinical trial based on Exhibit 1005?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. So I don't think that Exhibit 1005
9 is an exhaustive list of inclusion and
10 exclusion criteria for a specific patient, but
11 I think that a person of ordinary skill in the
12 arts reading this clinical trial would not
13 expect that they would be able to enroll a
14 nonmetastatic patient who had not failed prior
15 chemotherapy.
16 Q. You say that they would not expect
17 that a patient with nonmetastatic colorectal
18 cancer would be able to enroll in a study that
19 was proposed by Exhibit 1005, but would they
20 understand that that patient would necessarily
21 be excluded?
22 A. So I think a POSA would understand
23 that that patient would be excluded based on
24 the fact that it is not standard of care and
25

2 was not at that time to enroll a patient in
3 experimental clinic trial if they have
4 metastatic colorectal cancer and have not
5 received two lines of therapy or if they're
6 nonmetastatic and they could be cured by
7 surgery, the standard of care would be to take
8 them to surgery to remove their tumor.
9 Q. Are there nonmetastatic colorectal
10 cancers that cannot be cured by surgery?
11 A. So there are times where colorectal
12 cancer can grow locally to such an extent that
13 either it can't be cured by surgery or the
14 person is too sick and, therefore, they can't
15 undergo surgery.
16 Q. And I think you used the term
17 locally advanced cancer in your declaration to
18 describe those types of cancers; correct?
19 A. That is correct.
20 Q. Okay. So would a treating
21 oncologist who has a colorectal cancer patient
22 with locally advanced colorectal cancer expect
23 their patient to be excluded from the clinical
24 trial proposed by Exhibit 1005?

25 ATTORNEY RATLIFF: I object to the form

1 of the question.
2 A. So that's a much more complicated
3 group of patients, because a lot of it depends
4 on other factors. I think if you look at the
5 treatment guidelines, which we have from the
6 NCCN, they group together in many ways locally
7 advanced unreceptible patients and metastatic
8 patients. They're not -- excuse me, as I said
9 earlier, the exact same patient population.
10 There are other factors, including whether a
11 patient has measurable disease, based on
12 whether they have something that can be
13 measured on a CAT scan or by actual
14 measurements.
15 Q. So there is some group of
16 nonmetastatic colorectal cancers that a person
17 of ordinary skill would expect would be able
18 to be enrolled in the clinical trial proposed
19 by Exhibit 1005?
20 ATTORNEY RATLIFF: I object to the form
21 of the question, as well as to the premise of
22 the question.
23 A. So I think that a person of
24 ordinary skill would have to evaluate a
25

1 locally advanced nonmetastatic patient who has
2 already received and progressed in prior
3 therapy to determine if they would be suitable
4 for the trial based on their other treatment
5 options and whether this was possible.
6 Q. But there is nothing in
7 Exhibit 1005 that excludes that nonmetastatic
8 locally advanced colorectal cancer patient?
9 ATTORNEY RATLIFF: I object to the form
10 of the question.
11 A. So there are other criteria, of
12 course, in 1005 such as having measurable
13 disease, but if the person met all the other
14 criteria, this is not necessarily excluding
15 them if they have received two lines of prior
16 therapy and progressed, so just to add a
17 little clarity there I think I can.
18 So in general when we talk about
19 staging of colorectal cancer patients, if a
20 person has cancer that is initially locally
21 advanced and then it grows, it progresses on
22 chemotherapy, we generally think of that as
23 recurrent and, therefore, Stage 4 cancer or,
24 quote/unquote, metastatic.

1 So again, because this wouldn't be
2 appropriate for a newly diagnosed patient who
3 had not had chemotherapy, essentially everyone
4 who fit that criteria would be under the
5 category of metastatic.
6 Q. In your opinion, would a colorectal
7 cancer patient who had refused at least one
8 prior therapy qualify for the clinical trial
9 proposed by Exhibit 1005?
10 ATTORNEY RATLIFF: I object to the form
11 of the question.
12 A. So I think that if a patient met
13 the criteria in the NCCA guidelines for
14 clinical trial evaluation, they would be
15 appropriate for the trial, would be very
16 unusual to enroll a patient in a trial with an
17 experimental agent if we have effective
18 chemotherapy for that patient.
19 If for some reason that patient
20 cannot receive the chemotherapy, such as an
21 allergy to the medication or some other
22 disorder, then it would be reasonable to give
23 them the next available therapy, which is a
24 clinical trial.

Q. Okay. So a patient who had an allergy to the available chemotherapy would not be excluded from the clinical trial proposed in Exhibit 1005?

ATTORNEY RATLIFF: I object to the form of the question.

A. So there is not enough information in this trial to say whether that person would be included or excluded.

Q. But there is nothing in Exhibit 1005 that explicitly excludes someone who had refused chemotherapy because of an allergy?

ATTORNEY RATLIFF: I object to the form of the question.

A. So I would say for a person of ordinary skill in the art, we would generally not accept a patient on a clinical trial because they, quote, refused chemotherapy. It would only be appropriate if they could not receive the chemotherapy because of an allergy or some other life-threatening condition.

Q. But that patient who is otherwise qualified under the inclusion and exclusion

2 criteria in Exhibit 1005 would not be excluded
3 from this clinical trial if they had not
4 received a prior therapy because of an allergy
5 to the available chemotherapy?
6 ATTORNEY RATLIFF: I object to the form
7 of the question.
8 A. So I don't think a POSA can
9 determine if that person was excluded or based
10 on what's available in 1005.
11 Q. Why not?
12 A. Because it does not speak to that
13 point.
14 Q. Because it doesn't say anything
15 about prior therapies?
16 ATTORNEY RATLIFF: I object to the form
17 of the question, as well as to the premise of
18 the question.
19 A. So, again, a POSA reading this
20 clinical trial report would understand that a
21 patient with metastatic colorectal cancer is
22 only appropriate for clinical trial based on
23 current guideline or guidelines in July 2015
24 if they had failed first and second line

25 chemotherapy options, which are standard and

2 life prolonging options. They would not have
3 placed a person on a clinical trial such as
4 this if they didn't fit that criteria.
5 Q. So what do the guidelines say about
6 a colorectal cancer patient who those first
7 and second-line therapies are not available to
8 them because of let's say an allergy?
9 A. So I cannot think of an instance in
10 which a patient can receive either of those
11 chemotherapies because of an allergy. I think
12 it's possible that a person would have an
13 allergy to one of those medications and not be
14 able to receive it, but the standard of care
15 would be to give the medication that -- either
16 a modified dose or some way to try to overcome
17 that limitation. If there was absolutely no
18 way to give the chemotherapy, then that person
19 would be suitable for third line therapy
20 because they didn't have a second line option.
21 Q. And that third line therapy would
22 include clinical trials?
23 A. So according to the guidelines, it
24 would include consideration of a clinical
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25 trial.

ATTORNEY RATLIFF: Counsel, we've been going for an hour. Let's take a break.

ATTORNEY BROWN-MARSHALL: That's fine.

CERTIFIED STENOGRAPHER: Off the stenographic record at 2:12 p.m.

- - -

(Whereupon, a short recess was taken.)

- - -

CERTIFIED STENOGRAPHER: Back on the stenographic record at 2:28 p.m.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, I want you to assume that you are a GI oncologist who has a colorectal cancer patient that you would like to enroll in the study proposed by Exhibit 1005, okay?

A. Okay.

Q. Okay. And that colorectal cancer patient otherwise meets all the inclusion criteria, doesn't meet any of the exclusion criteria, and its enrollment has just begun, so there are open slots in all three of the arms of the proposed trial, okay?

1 ATTORNEY RATLIFF: I object to the
2 assumption that's leading up to this question.
3 A. I'm with you so far.
4 Q. Okay. You're with me?
5 A. Very hypothetical. Yes.
6 Q. Okay. So this hypothetical
7 colorectal cancer patient's tumor is tested
8 and they are determined to be MSI-high, would
9 that patient be enrolled in Arm 1 of the
10 proposed clinical trial?
11 ATTORNEY RATLIFF: I object to the form
12 of the question, as well as to the portion of
13 the question illuminating the hypothetical
14 parts of the question.
15 A. So can you tell me more about this
16 hypothetical question -- patient, sorry? What
17 age are they? What stage? What have they had
18 prior treatment with?
19 Q. Let's just assume that all of those
20 factors are such that they would qualify to be
21 in the clinical trial. So let's assume the
22 patient is qualified to be in the clinical
23 trial, okay? That colorectal cancer patient
24 is tested for MSI and tests positive for
25

2 MSI-high. They would be enrolled in Arm 1 of
3 the clinical trial; correct?
4 ATTORNEY RATLIFF: I object to the form
5 of the question.
6 A. So, again, I'm not following the
7 exact patient we're talking about. So can you
8 be a little clearer on what have they
9 previously been treated with? What else do we
10 know about them, etc.?
11 Q. So we don't need to know. They are
12 otherwise qualified. Whatever the
13 qualifications are, they've been enrolled in
14 the study.
15 ATTORNEY RATLIFF: I object to this
16 premise of we don't need to know.
17 Q. So let's assume that there is a
18 colorectal cancer patient who has qualified
19 and enrolled in the study proposed in
20 Exhibit 1005, their colorectal cancer is
21 tested and they are determined to be MSI-high,
22 which arm would they be enrolled in?
23 ATTORNEY RATLIFF: I object to the form
24 of the question.
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25 A. I'm really not sure what you're

2 trying to say, but I don't think a patient
3 could be enrolled in a trial without knowing
4 what arm they'd be enrolled into. So you
5 would need to have the MSI testing prior to
6 enrolling them in the trial. So I'm not clear
7 if you said that or not.
8 Q. Okay. So let's assume that you
9 have a colorectal cancer patient who is
10 MSI-high and who is enrolled in Arm 1 of the
11 proposed clinical trial, how would that
12 patient be treated?
13 ATTORNEY RATLIFF: I object to the form
14 of the question.
15 A. So in the arms of intervention
16 section of the clinical study record, it says
17 that: Expect numbers, that the MSI positive
18 colorectal cancer patient would be treated
19 with NK3475, which is pembrolizumab,
20 10 milligrams per kilogram every 14 days.
21 Q. Let's assume that you have a
22 colorectal cancer patient who is MS stable, so
23 not MSI-high, and who is enrolled in Arm 2 of
24 the proposed clinical trial, how would that

25 patient be treated?

2 A. So in the same table, an MSI
3 negative colorectal cancer patient would be
4 treated with MK3475, 10 milligrams per
5 kilogram every 14 times.
6 Q. And that's the same treatment as
7 the MSI-high colorectal cancer patient
8 enrolled in Arm 1; correct?
9 A. That is correct. It's called MSI
10 positive in this table, but yes.
11 Q. And, Dr. Oberstein, in your
12 declaration, you provide opinions regarding
13 JHU's evidence of secondary consideration; is
14 that correct?
15 ATTORNEY RATLIFF: I object to the form
16 of the question, as well as to the premise of
17 the question.
18 A. I'm sorry, can you repeat the
19 question?
20 Q. In your declaration, you provide
21 opinions regarding JHU's evidence of secondary
22 considerations; is that correct?
23 ATTORNEY RATLIFF: I object to the form
24 of the question, as well as to the premise of

25 the question.

2 A. So I do provide opinions regarding
3 JHU's alleged secondary considerations.
4 Q. Okay. What are secondary
5 considerations?
6 A. I understand that secondary
7 considerations are other things that might be
8 included to look for obviousness of a patent
9 claim, such as -- I don't recall what they
10 are, but a skepticism about the claim
11 treatment methods.
12 Q. So the secondary considerations
13 that you evaluated were skepticism --
14 A. I evaluated all the ones they
15 quoted. That's just the one that I mentioned
16 first.
17 Q. And how did you evaluate the
18 secondary considerations that you evaluated?
19 A. So as I detail, and I'm happy to go
20 through all of them, JHU's experts raised
21 several areas of secondary considerations.
22 One of them was that people were skeptical
23 about the claimed methods of treatment.
24 As I noted in Paragraph 180, I
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25 think that was a flawed comparison, of course,

2 because the critical time at which we're
3 evaluating this '393 patent is July 10, 2015,
4 and those discussions about skepticism that
5 happened on a personal level were from a very
6 different time period and were clearly not
7 reported for July 2015.
8 Q. So you're of the opinion evidence
9 of secondary considerations that is dated
10 prior to the priority date is relevant?
11 ATTORNEY RATLIFF: I object to the form
12 of the question.
13 A. That is not correct.
14 I think what's really important is
15 what the person of ordinary skill in the art
16 would have felt at the time of the priority
17 date, and there is no evidence of skepticism
18 at the time of the priority date.
19 On the contrary, there was a lot of
20 enthusiasm about doing this research as
21 evidenced by the fact that BMS and others had
22 started their own clinical trials testing
23 MSI-high colorectal cancer with PD-1
24 antibodies.
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25 Q. As of July 10, 2015, were results

2 available for the BMS clinical trial testing
3 MSI-high colorectal cancer that you mentioned?
4 A. There were no results that I know
5 of that were available. As you mentioned BMS,
6 there were, of course, results from a prior
7 single patient where MSI-high colon cancer was
8 treated with nivolumab, which was a drug made
9 by BMS, and a person of ordinary skill would
10 have known the public information that that
11 patient had a complete response after
12 treatment with PD-1 antibody.
13 Q. But that was a single patient;
14 correct?
15 A. That was a single patient with
16 MSI-high colorectal cancer.
17 Q. And as of July 10, 2015, were any
18 results available for the Merck clinical trial
19 in MSI-high colorectal cancers that you
20 mentioned?
21 A. Which Merck study? I'm sorry?
22 Q. Well, you cited a Merck study as
23 evidence that there would not be skepticism;
24 correct?
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25 A. So are you referring to

Exhibit 1148, Keynote 154.

Q. Is that the exhibit that you rely on?

A. Yes.

Q. Okay. So as of July 10, 2015, the Merck clinical trial that you rely on in Exhibit 1148 did not have results available; correct?

A. To the best of my knowledge, that is correct, but a person of ordinary skill would know, first of all, that Merck was conducting that study because of the public posting. They would also know about the BMS study. They would know about the single patient who had a complete response, and I think they would have utilized that information to be motivated to conduct this trial and to expect positive results from a clinical trial of a checkpoint blockade in MSI-high colorectal cancer.

Q. The ClinicalTrials.gov announcement that you rely on in conjunction with the Merck study that's dated May 29, 2015; correct?

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A. That is correct.

2 Q. Does that date ring a bell for you?
3 A. No.
4 Q. No?
5 That's also the date that the
6 results of the Hopkins trial that was proposed
7 in Exhibit 1005 were publicly announced?
8 ATTORNEY RATLIFF: I object to the form
9 of the question, as well as to the premise of
10 the question.
11 A. You mean the MSI-high study that
12 we've been discussing?
13 Q. I mean, the clinical trial that's
14 proposed in Exhibit 1005.
15 A. Correct.
16 Q. Okay. So the Merck trial was
17 announced the same day that the Hopkins
18 results were announced?
19 ATTORNEY RATLIFF: Wait. They're not
20 Hopkins results.
21 I object to the form of the question,
22 as well as the premise of the question.
23 A. So, again, I will restate it, but I
24 agree that the date that the -- this MSI study

25 results were initially announced was the same

1 date that Merck posted the second study on
2 ClinicalTrials.gov.
3 Q. And that second study posted by
4 Merck on ClinicalTrials.gov was a follow-up
5 study to the clinical trial proposed in
6 Exhibit 1005; correct?
7 ATTORNEY RATLIFF: I object to the form
8 of the question.
9 A. What do you mean by a follow-up
10 study?
11 Q. That Merck study that was proposed
12 in Exhibit 1148 followed on the results of the
13 Johns Hopkins study proposed in Exhibit 1005;
14 correct?
15 ATTORNEY RATLIFF: I object to the form
16 of the question.
17 A. So I don't know what motivation
18 Merck had in doing that study or what they
19 included in the submission. In Exhibit 1148
20 they proposed a study of the MSI-high
21 colorectal cancer and proposed treating those
22 patients with pembrolizumab.
23 ATTORNEY BROWN-MARSHALL: I'd like to
24 mark as Exhibit 2061.
25

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 - - -
3 (Whereupon, Merck document JHU2061,
4 is received and marked as Exhibit 2061 for
5 Identification.)
6 - - -
7 CERTIFIED STENOGRAPHER: Number 2061.
8 BY ATTORNEY BROWN-MARSHALL:
9 Q. And, Dr. Oberstein, are you
10 familiar with this exhibit?
11 ATTORNEY RATLIFF: And I'll object to
12 Exhibit 2061 for the purposes of
13 authentication, foundation, and hearsay.
14 A. I am not familiar with this press
15 release.
16 Q. Okay. And does this appear to be a
17 Merck news release, dated May 29, 2015?
18 A. Yes, it does.
19 Q. And do you see about two-thirds of
20 the way down where it says: Merck, NYSE:MRK,
21 known as MSD outside the United States and
22 Canada, today announced results from the first
23 study evaluating the correlation of benefit
24 with an immunotherapy based on DNA mismatch
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25 repair, MMR, deficiency, a well-established

2 form of genetic instability in many cancers
3 characterized by the loss of function of the
4 MMR pathway.
5 Do you see that?
6 A. I do see that, yes.
7 Q. And then it says: The Phase II
8 study led by researchers from Johns Hopkins
9 Kimmel Cancer Center evaluated Merck's
10 anti-PD-1 therapy, Keytruda pembrolizumab, in
11 48 valuable heavily pretreated patients with
12 advanced colorectal cancer and other solid
13 tumors.
14 Do you see that?
15 A. I do see that.
16 Q. And do you understand that this
17 news release is referring to the results of
18 the clinical trial proposed in Exhibit 1005?
19 A. Yes.
20 Q. And if you would turn to Page 2 and
21 then the first full paragraph, do you see
22 where it says: Based on the encouraging
23 results of this early study, Merck will
24 initiate a registration Phase II study Keynote

25 164 to evaluate the efficacy and safety of

1 Keytruda based on mismatch repair status and
2 locally advanced unreceptible or metastatic
3 Stage 4 colorectal cancers.
4 Do you see that?
5 ATTORNEY RATLIFF: You read that
6 incorrectly. I object to the form of the
7 question.
8 A. I do see that statement, that
9 sentence.
10 Q. Okay. Is that Phase II study
11 Keynote 164, is that the study proposed in
12 Exhibit 1148 that you rely on?
13 A. Yes, it is.
14 Q. Okay. And the press release
15 indicates that that study proposed in
16 Exhibit 1148 is based on the encouraging
17 results of this early study; correct?
18 A. The press release does say that,
19 yes.
20 Q. And this early study that it's
21 referring to is the study led by Johns Hopkins
22 University proposed by Exhibit 1005; correct?
23 A. That's correct.
24 Q. Okay. And if you look at the next
25

2 paragraph, there is a quote from Dr. Roger
3 Dansey, therapeutic area head and senior
4 vice-president oncology, late stage
5 development, Merck Research Laboratories.
6 Do you see that?
7 A. I see that.
8 Q. Okay. And Dr. Dansey says: These
9 exciting results, while early, suggest that
10 evidence of DNA mismatch repair deficiency may
11 be an important way of identifying tumors that
12 are responsive to checkpoint blockade.
13 Do you see that?
14 A. I see that.
15 Q. So Dr. Dansey didn't say that DNA
16 mismatch repair deficiency is conclusively a
17 way of identifying tumors that are responsive
18 to checkpoint blockade; correct?
19 ATTORNEY RATLIFF: Are you asking about
20 in this article or if he's ever said that?
21 ATTORNEY BROWN-MARSHALL: I'm asking
22 about in this article.
23 A. So I didn't read the rest of the
24 article. I'm just seeing this for the first

25 time. The sentence you just read uses the

2 word "maybe."

3 Q. Maybe.

4 And Dr. Dansey goes on to say that:

5 DNA mismatch repair deficiency is an

6 established biomarker in many types of cancer,

7 and these results open the door for research

8 with Keytruda in colorectal cancer and other

9 tumor types with this potentially clinical

10 meaningful tool.

11 Do you see that?

12 A. I see that.

13 Q. So at this point on May 29, 2015,

14 DNA mismatch repair deficiency is not an

15 established biomarker for treatment with

16 Keytruda in colorectal cancer; correct?

17 ATTORNEY RATLIFF: I object to the form

18 of the question.

19 A. So I'm not sure why you say that.

20 Q. Uh-huh.

21 A. Where does this indicate anything

22 about whether Keytruda is an established

23 biomarker for -- whether mismatch repair

24 deficiency is an accomplished biomarker for

25 treatment with Keytruda?

2 Q. Well, according to Dr. Dansey, DNA
3 mismatch repair deficiency is a potentially
4 clinically meaningful tool; correct?
5 A. Correct.
6 Q. And he goes on to say: We look
7 forward to initiating a registration Phase II
8 study of Keytruda in patients with colorectal
9 cancer to further explore this genomic
10 biomarker; correct?
11 ATTORNEY RATLIFF: You read that
12 incorrectly. I object to the form of the
13 question.
14 ATTORNEY BROWN-MARSHALL: Okay. I'll
15 read it again.
16 Q. We look forward to initiating a
17 registrational Phase II study of Keytruda in
18 patients with colorectal cancer to further
19 explore this genomic biomarker; correct?
20 A. That is what is written here, yes.
21 Q. Yes. He didn't say that they were
22 applying for FDA approval for treating
23 colorectal cancer based on DNA mismatch repair
24 deficiency at this point; correct?

25 ATTORNEY RATLIFF: I object to the form

1 of the question.
2 A. He did not say that.
3 Q. He said: We'll be further
4 exploring this genomic biomarker?
5 A. So, again, I did not conduct my
6 analysis based on the date of May 29, 2015,
7 but based on July 10, 2015, I concluded and
8 stand by that a person of ordinary skill in
9 the art would look at the available data,
10 including the trial reports, trial records,
11 the report of the one patient who succeeded,
12 and would be motivated to conduct clinical
13 trial -- conduct, sorry, therapy of a patient
14 with MSI-high colorectal cancer with a
15 reasonable expectation of success. I assume
16 Dr. Dansey assumed that as well, but I do not
17 speak from his perspective.
18 Q. Had the Merck trial proposed in
19 Exhibit 1148 enrolled any patients as of
20 July 10, 2015?
21 A. I don't know. I did not make any
22 representations about enrollment on these
23 trials.
24 Q. So it's just the initiation of that
25

1 trial described in Exhibit 1148 that you're
2 relying on?
3 A. So I don't think I relied on the
4 initiation either. I relied on the
5 publication of the plan to do that trial,
6 which would have been available to a person of
7 ordinary skill in the arts and would have
8 given that person motivation to conduct a
9 trial according to what was described in the
10 MSI study record, and to expect positive
11 results if they follow the methods of this
12 trial to achieve positive results from
13 treatment of patients with MSI-high colorectal
14 cancer with pembrolizumab.
15 Q. Did you investigate at all the
16 status of Merck's trial proposed in
17 Exhibit 1148 as of July 10, 2015?
18 A. Your question is did I investigate
19 whether it was enrolling patients?
20 Q. The status?
21 A. I do not recall doing that. Again,
22 the reason I reference that study and what
23 reported from is that it was available
24 publicly to a person of ordinary skill and
25

they would have been motivated by that report to want to conduct a study, treat a patient, and expect a positive result.

Q. And by "that report," you're talking about the preliminary submission to ClinicalTrials.gov in Exhibit 1148?

A. I'm referring to the submission in 1148. I'm not sure why you're calling it preliminary, but that is the exhibit I'm referring to.

Q. If you would, Dr. Oberstein, go to Paragraph 183 in your declaration, and if you see about halfway down you write: While Dr. Le did not provide any additional details regarding her alleged observations for when Merck's funding began, this purported evidence is from the time period of the start of the MSI-high study, more than two years before July 10, 2015.

Do you see that?

A. Yes, I see that.

Q. Okay. And you reviewed Dr. Le's declaration; correct?

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A. Yes, I did.

2 Q. Okay. Did you review the exhibits
3 that she cited in her declaration?
4 A. I believe so, but I might have to
5 be refreshed on some of them.
6 Q. And you're engaged as an expert by
7 Merck in this case; correct?
8 A. That is correct.
9 Q. And did you ask Merck when it first
10 funded Dr. Le's study?
11 ATTORNEY RATLIFF: Object.
12 Hold on.
13 Object to the form of the question, as
14 well as to the premise of the question.
15 A. I did not.
16 Q. Okay. Do you believe Merck would
17 have kept records of any funding that it
18 provided for Dr. Le's study?
19 ATTORNEY RATLIFF: I object to the form
20 of the question, as well as to the premise of
21 the question.
22 A. So I'm really not familiar with how
23 Merck keeps records.
24 Q. Uh-huh.

25 A. I don't know how long they retain

1 them or where those things are.
2 Q. Uh-huh.
3 A. So I'm familiar with those records.
4 Q. Did Merck or Merck's attorneys
5 provide you with any documentation that showed
6 when they provided the first payments for
7 Dr. Le's study?
8 ATTORNEY RATLIFF: I object to the form
9 of the question. I don't even know what
10 Dr. Le's study is.
11 A. So I don't recall seeing any
12 documentation from my attorneys or from Merck
13 about their funding or provision of drug for
14 the MSI study.
15 Q. All right.
16 ATTORNEY BROWN-MARSHALL: I'd like to
17 mark as Exhibit 2131.
18 - - -
19 (Whereupon, document JHU2131, is
20 received and marked as Exhibit 2131 for
21 Identification.)
22 - - -
23 CERTIFIED STENOGRAPHER: Number 2131.
24 THE WITNESS: Thank you.
25

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 BY ATTORNEY BROWN-MARSHALL:
3 Q. And, Dr. Oberstein, I'll represent
4 to you that this is one of the exhibits Dr. Le
5 relied on in her declaration.
6 A. Okay.
7 Q. Okay?
8 And do you see on the first page
9 where it says: Investigator initiated
10 clinical trial research agreement?
11 Do you see that?
12 A. Yes, I see that.
13 Q. Okay. Did you review this document
14 in preparing your declaration?
15 A. I don't recall.
16 Q. Okay. And if you would just flip
17 to the back page, last page of the exhibit.
18 Do you see that there are some signatures?
19 A. Yes.
20 Q. And you see at the bottom it's
21 signed by Dr. Dung Le, M.D., principal
22 investigator?
23 A. Yes.
24 Q. Do you see that? Okay.
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25 And then the line above, it's also

1 signed by a representative of the Johns
2 Hopkins University, the associate dean of
3 research administration.
4 Do you see that?
5 A. Yes.
6 Q. And then it's also signed by Eric
7 H. Rubin, M.D., on behalf of Merck Sharp &
8 Dohme.
9 Do you see that?
10 A. Yes.
11 Q. And you did not review this exhibit
12 in preparing your declaration?
13 A. I do not recall.
14 Q. All right.
15 ATTORNEY BROWN-MARSHALL: I'd like to
16 mark as Exhibit 2408.
17 - - -
18 (Whereupon, document entitled
19 Amendment #1, is received and marked as
20 Exhibit 2408 for Identification.)
21 - - -
22 CERTIFIED STENOGRAPHER: Number 2408.
23 BY ATTORNEY BROWN-MARSHALL:
24 Q. And, Dr. Oberstein, are you
25

1 familiar with this document?

2 ATTORNEY RATLIFF: And I object to

3 Exhibit 2048 --

4 THE WITNESS: 2408.

5 ATTORNEY RATLIFF: Thank you.

6 I object to Exhibit 2408 for purposes

7 of authentication, foundation, and hearsay.

8 A. I do not recall looking at this

9 document.

10 BY ATTORNEY BROWN-MARSHALL:

11 Q. Okay. So you didn't review this

12 document in preparing your -- strike that.

13 You did not review Exhibit 2408 in

14 formulating your opinions in your declaration;

15 correct?

16 A. I do not recall doing that.

17 [redacted]

18 [redacted]

19 [redacted]

20 [redacted]

21 A. I see that, yes.

22 ATTORNEY BROWN-MARSHALL: I'd like to

23 mark as Exhibit 2409.

24 - - -

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25 (Whereupon, document entitled

1 Amendment #2, is received and marked as
2 Exhibit 2409 for Identification.)
3 - - -
4 CERTIFIED STENOGRAPHER: Number 2409.
5 BY ATTORNEY BROWN-MARSHALL:
6 Q. Dr. Oberstein, are you familiar
7 with Exhibit 2409?
8 ATTORNEY RATLIFF: I object to
9 Exhibit 2409 for the purposes of
10 authentication, foundation, and hearsay.
11 A. So can I just ask was this included
12 in Dr. Le's declaration?
13 Q. No, it was not.
14 A. So I'm not familiar with it.
15 [redacted]
16 [redacted]
17 [redacted]
18 [redacted]
19 A. I do not believe so.
20 Q. And Merck's attorneys did not
21 provide this document to you?
22 A. I do not recall ever seeing it
23 before.
24 ATTORNEY BROWN-MARSHALL: I'd like to
25 mark as Exhibit 2410.

1 02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240
2 - - -
3 (Whereupon, document entitled
4 Amendment #3, is received and marked as
5 Exhibit 2410 for Identification.)
6 - - -
7 CERTIFIED STENOGRAPHER: Number 2410.
8 BY ATTORNEY BROWN-MARSHALL:
9 Q. And, Dr. Oberstein, are you
10 familiar with Exhibit 2410?
11 ATTORNEY RATLIFF: And I'll object to
12 Exhibit 2410 for the purposes of
13 authentication, foundation, and hearsay, and,
14 counsel, do you have another copy of 2410?
15 ATTORNEY BROWN-MARSHALL: Oh,
16 apologies.
17 A. I am not familiar with this
18 document.
19 [redacted]
22 A. Correct.
23 [redacted]

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[redacted]

A. I do see that, yes.

[redacted]

A. Yes, I do.

Q. Okay. And do you see where it lists first payment?

A. Yes.

[redacted]

ATTORNEY RATLIFF: I object to the form of the question.

[redacted]

[redacted]

ATTORNEY RATLIFF: I object to the form of the question.

A. That's correct.

ATTORNEY BROWN-MARSHALL: And also I'd like to note for the record that we'd like to designate Exhibits 2408, 2409, and 2410 as confidential under the protective order.

2 Q. You can put that aside,
3 Dr. Oberstein.
4 Dr. Oberstein, if you would turn to
5 Paragraph 182 of your declaration. And in the
6 second sentence you write: Dr. Lonberg points
7 to the earlier study of BMS's anti-PD-1 drug
8 that led to a complete response in an MSI-high
9 colorectal cancer patient and reported in
10 Lipson in January 2013 as a comparison to
11 assert that the results the MSI-high study
12 were unexpected because the BMS study failed
13 to produce a response in 32 of 33 patients
14 with colorectal cancer; is that correct?
15 A. That is what it says.
16 Q. Okay.
17 A. I disagree with that statement, but
18 that's what it says.
19 Q. Okay. So in the BMS clinical trial
20 with this drug nivolumab, they reported one
21 complete response in an MSI-high colorectal
22 cancer patient; correct?
23 A. That is correct.
24 Q. And they also reported that it
25 failed to produce a response in 32 of 33

2 patients with colorectal cancer; correct?
3 A. Correct. 33 patients were treated.
4 Only one responded and that one had MSI-high
5 colorectal cancer.
6 Q. Okay. What was the MSI status of
7 the other 32 patients who didn't respond?
8 A. I don't believe that was reported
9 by BMS.
10 Q. Okay. So that was not known at the
11 time?
12 A. I don't believe it was known at the
13 time.
14 Q. Okay. All right.
15 If you would turn to Paragraph 185
16 of your declaration.
17 A. I'm there.
18 Q. Okay. And in this paragraph, you
19 are providing opinions on Dr. Goldberg's
20 evidence of a long-felt, unmet need; correct?
21 ATTORNEY RATLIFF: I object to the form
22 of the question.
23 A. His alleged evidence as I outline,
24 yes.
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25 Q. What is a long-felt, unmet need?

2 A. A long-felt, unmet need is a sense
3 among the person of ordinary skill in the art
4 and relevant stakeholders that there is no
5 effective or not adequate effective treatments
6 for a certain condition.
7 Q. And you write that: Dr. Goldberg
8 discusses chemotherapy and targeted therapies
9 available in 2010 to 2015, but does not tie
10 any of this evidence to any of the patent
11 claims; correct?
12 A. That is correct.
13 Q. Why would evidence of chemotherapy
14 and targeted therapies available in 2010 to
15 2015 need to be tied to any of the patent
16 claims?
17 A. So Dr. Goldberg is proposing
18 secondary considerations and proposes that
19 they justify or help speak to the
20 nonobviousness of the patent claims. He
21 doesn't discuss or connect them to any of the
22 patent claims.
23 Q. Well, chemotherapy and targeted
24 therapy as available in 2010 to 2015, those
25 are therapies that are described in the prior

2 art; correct?

3 A. That is correct.

4 Q. Okay. Why would you need to tie

5 the prior art to the patent claims in order to

6 demonstrate a long-felt, unmet need?

7 A. So the long-felt, unmet need for

8 certain treatment should be relevant to the

9 treatment that you are going to propose to

10 fill that unmet need.

11 And I think that the person of

12 ordinary skill in the art who would have

13 access to MSI-high study record and prior art

14 references that suggest that immunotherapy

15 will be effective in MSI-high colon cancer

16 would anticipate that pembrolizumab or PD-1

17 antibodies would be effective and would be

18 worth conducting a trial to test in MSI-high

19 colorectal cancer with an expectation of

20 success. Chemotherapy and other therapies are

21 not relevant to that specific type of therapy.

22 Q. So as of July 10, 2015, what

23 therapies were available for treating

24 colorectal cancer?

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25 A. So Dr. Goldberg goes through a lot

2 of those, but they were essentially
3 chemotherapies and several targeted therapies,
4 as well as some other therapies that fall into
5 the greater rubric of targeted therapy, but a
6 person of ordinary skill in the art as of
7 July 10, 2015 would have been aware of the
8 MSI-high study record, the previous art
9 references, and would have been motivated to
10 treat an MSI-high colorectal cancer patient
11 with pembrolizumab with a reasonable
12 expectation of success.
13 Q. So as of July 10, 2015, Keytruda
14 had not received FDA approval for treatment of
15 any MSI-high cancers; correct?
16 A. That is correct.
17 Q. And as of July 10, 2015, Merck had
18 made zero net sales of Keytruda for colorectal
19 cancer patients; correct?
20 A. So I don't know that, but I -- I
21 don't know that.
22 Q. Okay. Did you speak with
23 Dr. Sheridan about his analysis of the sales
24 of Keytruda for colorectal cancer?
THE SULLIVAN GROUP OF COURT REPORTERS
25 A. I did not.

Q. And as of July 10, 2015, BMS's nivolumab had not received FDA approval for treatment of -- of any MSI-high cancers; correct?

A. That is correct.

Q. Okay. So any prescription of either Keytruda or nivolumab as of July 10, 2015 would have to be an off-label prescription; correct?

A. So I think a person of ordinary skill in the art might have contemplated treating a patient off-label, but more accurately they would have tried to enroll a patient in a clinical trial such as that described in the MSI study record to follow those methods to treat a patient who has MSI colorectal cancer with a therapeutic dose of pembrolizumab or nivolumab.

Q. But those clinical trials are limited in the number of patients that can be treated under that; correct?

A. Correct.

Q. So those therapies are not available to patients outside of the clinical

1 trials; correct?
2 ATTORNEY RATLIFF: I object to the form
3 of the question.
4 A. So a clinical trial is not
5 available outside of a clinical trial. There
6 are therapies, of course, that are available
7 off-label as you say.
8 Q. And any prescription of either
9 Keytruda or nivolumab outside of the clinical
10 trial as of July 10, 2015 would have to be
11 off-label; correct?
12 ATTORNEY RATLIFF: For any use? I
13 object to the form of the question.
14 A. So there were FDA approved
15 indications of pembrolizumab as of July 10,
16 2015.
17 Q. So any prescription of either
18 Keytruda or nivolumab for a patient with
19 MSI-high colorectal cancer outside of a
20 clinical trial as of July 10, 2015 would have
21 to be off-label; correct?
22 A. That is correct.
23 Q. Dr. Oberstein, did you review any
24 statements by Merck to the FDA regarding
25

1 metastatic MSI-high colorectal cancer patients
2 representing a group of patients with a high
3 unmet medical need?
4 A. I don't recall.
5 ATTORNEY BROWN-MARSHALL: If you want,
6 we can take a short break, and I can figure
7 out if I have any additional questions?
8 ATTORNEY RATLIFF: Sure.
9 CERTIFIED STENOGRAPHER: Off the
10 stenographic record at 3:09 p.m.
11 - - -
12 (Whereupon, a short recess was
13 taken.)
14 - - -
15 CERTIFIED STENOGRAPHER: Back on the
16 stenographic record at 3:20 p.m.
17 BY ATTORNEY BROWN-MARSHALL:
18 Q. Dr. Oberstein, is it your opinion
19 that as of July 10, 2015, metastatic MSI-high
20 colorectal cancer patients did not represent a
21 group of patients with a high unmet medical
22 need?
23 A. So that is not my opinion. I think
24 that MSI -- I'm sorry, MSI-high colorectal
25

1 cancer?
2 Q. Yes.
3 A. So I think that as of July 10,
4 2015, MSI-high colorectal cancer patients did
5 qualify as a high unmet need. That was the
6 question?
7 Q. Yes.
8 ATTORNEY BROWN-MARSHALL: I have no
9 further questions.
10 Thank you for your time today.
11 THE WITNESS: Okay.
12 ATTORNEY RATLIFF: So, Doctor, I do not
13 have any questions for you.
14 However, I request that this transcript
15 be designated highly confidential under the
16 protective order, and, counsel, we can work
17 out what portions should be not under the
18 confidentiality of the protective order.
19 We're done.
20 (Continued on next page for jurat.)
21
22
23
24
25

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1
2 CERTIFIED STENOGRAPHER: Off the
3 stenographic record at 3:21 p.m.
4 - - -
5 (Time noted: 3:21 p.m.)
6 - - -
7
8 _____
PAUL E. OBERSTEIN, M.D.
9 Subscribed and sworn to before me
10 this _____ day of _____ 2025.
11
12
13 _____
Notary Public
My Commission Expires:
14
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1

2 C E R T I F I C A T E

3 I, RICHARD GERMOSEN, Fellow of the

4 Academy of Professional Reporters, stenographic New

5 Jersey Certified Court Reporter, New Jersey Certified

6 Realtime Court Reporter, California Certified

7 Shorthand Reporter, California Certified Realtime

8 Reporter, NCRA Registered Diplomate Reporter, and

9 NCRA Certified Realtime Reporter, do hereby certify:

10 That PAUL E. OBERSTEIN, M.D., the

11 witness whose deposition is hereinbefore set forth,

12 having been duly sworn, and that such deposition is

13 a true record of the testimony of said witness.

14 I further certify that I am not related

15 to any of the parties to this action by blood or

16 marriage, and that I am in no way interested in the

17 outcome of this matter.

18 IN WITNESS WHEREOF, I have hereunto set

19 my hand this 20th day of February 2025.

20

21 _____

22 RICHARD GERMOSEN,
FAPR, RDR, CRR, CCR-NJ, CRCR, CSR-CA, CCRR-CA,
23 NYACR, NYRCR
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24 LICENSE NO. 30XR00016800
California CSR No. 14391
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25 California CRR No. 198