UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HIGHLY CONFIDENTIAL | PROTECTIVE ORDER

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MERCK SHARP & DOHME LLC,

Petitioner,

-against-

THE JOHNS HOPKINS UNIVERSITY,

Patent Owner.

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

STENOGRAPHIC DEPOSITION OF:
PAUL E. OBERSTEIN, M.D.
Wednesday, February 19, 2025
7:59 a.m. - 3:21 p.m. | Pages 1 - 320

Reported stenographically by:
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RDR, CRR, CCR, CRCR, CSR-CA, NYACR, NYRCR
NCRA/NJ/NY/CA Certified Realtime Reporter
NCRA Realtime Systems Administrator
Job No. J12413091
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JHU 2404
Merck Sharp v. Johns Hopkins
IPR2024-00623

STENOGRAPHIC DEPOSITION on behalf of Patent Owner of PAUL E. OBERSTEIN, M.D., taken in the above-entitled matter before RICHARD GERMOSEN, Fellow of the Academy of Professional Reporters, Certified Court Reporter, (License No. 30XI00184700), Certified Realtime Court Reporter-NJ, (License No. 30XR00016800), California Certified Shorthand Reporter, (License No. 14391), NCRA/NY/CA Certified Realtime Reporter, NCRA Registered Diplomate Reporter, New York Association Certified Reporter, NCRA Realtime Systems Administrator, taken at the offices of PAUL HASTINGS LLP, MetLife Building, 200 Park Avenue, New York, New York 10166, on Wednesday, February 19, 2025, commencing at 7:59 a.m.

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I N D E X

WITNESS	EXAMINATION
PAUL E. OBERSTEIN, M.D.	
BY ATTORNEY BROWN-MARSHALL	8

E X H I B I T S

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

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

02.19.2025 Deposition of Paul E. Oberstein, M.D.
IPR2024-00240

P R O C E E D I N G S

7:59 a.m.

CERTIFIED STENOGRAPHER: On the stenographic record 7:59 a.m.

Good morning. My name is Rich Germosen. I am a Certified Stenographic Reporter. My license is available for inspection.

- - -

(Whereupon, the Certified Stenographic Reporter administered the oath to the witness.)

- - -

P A U L E. O B E R S T E I N, M.D.,

(the witness produced a New York State driver's license), having been first duly sworn or affirmed, was examined and testified as follows:

EXAMINATION BY ATTORNEY BROWN-MARSHALL:

BY ATTORNEY BROWN-MARSHALL:

Q. Good morning, Dr. Oberstein.

A. Good morning.

Q. Would you please state your full

name and address for the record.

A. Paul Eliezer Oberstein, 644 West 232nd Street, Bronx, New York.

Q. And, Dr. Oberstein, have you been deposed before?

A. I have been deposed before, yes.

Q. Okay. How many times?

A. As far as I recall, just one time.

Q. Okay. And what sort of matter was that deposition related to?

A. As I recall, it related to a medical malpractice case.

Q. And were you serving as an expert in that case?

A. I was not serving as an expert.

Q. Were you a fact witness in that case?

A. I was a party in that case.

Q. Okay. And you understand that you are here testifying today under oath; correct?

A. That's correct.

Q. Okay. And that you understand that according to that oath, you are required to tell the truth, the whole truth, and nothing

but the truth; correct?

A. Yes.

Q. And will you do that?

A. Yes.

Q. The court reporter here is taking down everything that I say and that you say, so we need to make sure that we speak loudly and clearly and not speak over each other.

Is that understandable?

A. Yes.

Q. And now, I'm planning to take a break probably about every hour or so, but if you need to take a break before that, just let me know, but the one thing that I ask is that if there is a question pending, please answer the question, and then we can take a break after that, okay?

A. Sounds good.

Q. Is there any reason why you can't give your best testimony today?

A. No.

Q. Okay. No medications that might interfere with your ability to give your best testimony?

A. No.

Q. No car accidents on the way to the deposition?

A. No.

Q. Okay. Have you previously served as an expert in a legal matter before?

A. Yes, I have.

Q. Okay. Was that a patent-related matter?

A. So I have served in a patent-related matter, yes.

Q. Okay. And just generally, what sort of technology was that related to?

A. The patent matter was related to a medication, a pharmaceutical drug.

Q. Okay. What type of drug?

A. Can you clarify the question?

Q. Well, you said it was related to a pharmaceutical or a drug. Just generally what type of drug?

A. It was a chemotherapy agent.

Q. Okay. But you weren't deposed in that matter in which you served as an expert?

A. Correct. I -- I did some

preliminary work with the company -- with a law firm, but did not lead to a deposition yet.

Q. Okay. So it's an ongoing matter?

A. It is an open matter, yes.

Q. Okay. And do you anticipate that you will be filing an expert report in that matter?

A. So I don't know yet. I've not begun such a report or received an assignment to do that.

Q. Okay. And as a part of your work as an expert in that matter, have you been asked to review any patents?

A. Yes, I reviewed patents in that matter.

Q. Okay. Are you the inventor on any patents?

A. Not that I'm aware of.

Q. Okay. Have you previously worked on any projects that resulted in patents being issued?

A. So I partly answered the previous question vaguely, because I presume so, but

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?

Q. Well, you said you're familiar with the process. I just want to know sort of at a high level what your understanding is of what that process is.

A. So my understanding is that a group of proposed inventors will submit a patent to the Patent Office and the Patent Office will then evaluate that patent and make a determination about patentability. I also understand from reviewing this case that others can then challenge the patent, and there are times where it will come back and be revisited.

Q. And what sort of challenges do you understand that can be made to a patent that's already issued?

A. So I understand from this case that some challenges to a patent may be issued if the patent is anticipated in the prior art or is obvious from the prior art. I'm sure there are many other reasons why such things can be challenged.

- - -

(Clarification requested by the

stenographer.)

- - -

A. Why a patent can be challenged, but those are the ones I'm familiar with from this case.

Q. And you mentioned anticipation. What is anticipation?

A. So as I understand, anticipation is where the claims of the patent are previously reported in a prior work of art that would be publicly available.

Q. And you also mentioned obviousness. What is your understanding of obviousness?

A. So my understanding of obviousness is that a person of ordinary skill of the art with the prior art references might be able to deduce all of the claims within the patent.

Q. And, Dr. Oberstein, you understand that you are testifying today as an expert in an inter partes review proceeding or IPR proceeding; correct?

A. Yes, I understand that.

Q. Okay. And you understand that IPR proceedings, including deposition transcripts,

are public; correct?

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

A. So I am not aware of that and I don't know if that's true.

Q. Okay. And did counsel inform you that the transcript from this deposition will be publicly available on the USPTO website?

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

A. That is not something I ever discussed with my counsel.

Q. And before we get started, Dr. Oberstein, I notice that you have several piles of documents in front of you. What are those documents?

A. So I have several. I have my rebuttal declaration that I submitted in this patent case. I have a copy of the '393 patent, the MSI study record, several declarations, including from Dr. Lonberg, Dr. Goldberg, Dr. Le, and Dr. Pardoll, as well as Dr. Neugut, and then several -- actually,

six source articles that I reference in my declaration.

Q. Okay. And which articles are those?

A. So these are articles by Steinert; Champiat; Chapelle; Benson, sorry, there are seven. Hamid, Pernot, and Salipante.

Q. And are those clean copies or do those copies have any sorts of annotations on them?

A. These copies do not have any annotations.

Q. So they're all clean copies?

A. Of the articles?

Q. Of all of those documents?

A. So everything is clean. I have several stickies, Post-its in my rebuttal declaration.

Q. And where are those stickies located?

A. So I have three. Two of them are next to exhibits in the appendix. One is Exhibit 1135 and one is Exhibit 1137.

Q. Why do you have stickies next to

Exhibit 1135 and 1137?

A. So I place notes next to those because in my review of my declaration, I noted that I had not actually reviewed the depositions prior to signing my declaration. I had reviewed the declarations of those names, people, but I confused it and wrote "deposition" by mistake.

Q. Okay.

A. So I'd like to remove those essentially.

Q. Okay. And which depositions are those?

A. That was one, 1135 was the deposition of Jennifer Newberger.

Q. Okay.

A. And Exhibit 1137 was a deposition of Brian Segers.

Q. So you did not review the deposition transcripts of Ms. Newberger or Dr. Segers?

A. Correct, but I reviewed their declarations, which was my mistake.

Q. And I see that you have at least

one other sticky note in there.

A. Yes.

Q. What is that one?

A. I have one other sticky note, which is in Paragraph 188 of my declaration, where I wrote that my opinion is consistent with Dr. Neugut's declaration and deposition testimony. I had not -- as I recalled, had not reviewed Dr. Neugut's deposition prior to signing this declaration -- my declaration. I have subsequently reviewed it and it was available to me, but I had not reviewed it yet by the time I signed the declaration.

Q. Okay.

A. My review of that deposition has not changed any of my opinions in this case.

Q. Okay. So you'd like to make a correction to Paragraph 188 to remove the mention of Dr. Neugut's deposition; correct?

A. Correct.

Q. Okay. Are there any other changes that you would like to make to your declaration?

A. There are none that I would like to

make or none that I'm aware of that need to be made.

Q. And, Dr. Oberstein, when were you first engaged to work on this case?

A. Can you define "engaged" perhaps?

Q. Well, let's start: When were you first contacted with respect to this case?

A. So as I recall, I was first contacted in the summer of 2024, this past summer, about potentially consulting in regards to this case.

Q. And who contacted you in the summer of 2024?

A. So I apologize, I'm very poor with name recollection, but an attorney from the Paul Hastings law firm or perhaps it wasn't an attorney. A representative from the Paul Hastings law firm.

Q. And that representative, is that one of the attorneys present here today?

A. I do not believe that the initial contact was from one of the people present today.

Q. Is it a male or a female attorney?

A. I don't recall. It was an email.

Q. An email.

And when did you first speak with someone from the Paul Hastings law firm about this case?

A. So shortly after that initial contact, when I expressed an interest in speaking, I had a telephone conference with members of the Paul Hastings law firm.

Q. And which members were those?

A. I don't recall the names.

Q. Are they one of the attorneys that are present here today?

A. I believe several of the attorneys here today may have been part of that, but I don't recall exactly.

Q. And have you signed a formal engagement letter with respect to your work in this case?

A. Had I or have I?

Q. Have you?

A. I have, yes.

Q. Okay. And approximately when did you sign that engagement letter?

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.

I recall that they discussed with

me that there is a patent about a purported method of treatment and that there were prior art documents that discuss some of the factors in the patent, and they wanted to know if I could evaluate those and give an assessment as to whether the claims of the patent were previously revealed in the prior art references or -- or previously taught by the MSI study record.

Q. Was Dr. Neugut involved in that conversation?

A. No.

Q. Are you acquainted with Dr. Neugut?

A. What do you mean by "acquainted"?

Q. Do you know each other?

A. I do know Dr. Neugut. I haven't seen him in quite some time, but I do know of him and do know him.

Q. Okay. Have you spoken to Dr. Neugut about any of the matters involved in this case?

A. I have not.

Q. How many hours have you worked on this case?

A. So I don't have an exact number of hours. I estimate somewhere in the range of 30 to 50 hours in review of all the documents, declarations, and depositions in preparation of my declaration, but I certainly do plan to sit down and tally it up. I don't have that exact number right now.

Q. And that 30 to 50 hours, does that -- is that the number of hours that you've billed for this case?

A. So no, that is not.

Q. That is not?

A. (Indicating.)

Q. Okay. How many hours have you billed on this case?

A. Again, I don't have an exact number, but I think I billed somewhere between 20 to 25 hours so far for the work that I've done, and obviously have more to submit.

Q. So 20 to 25 is the number that you've currently submitted bills for. You have outstanding hours that you haven't billed for yet?

A. Correct.

Q. And if you add up those currently billed, plus outstanding billed, that would total that 30 to 50 hours of work that you previously estimated --

A. That's what I estimated, yes.

- - -

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

- - -

CERTIFIED STENOGRAPHER: "30 to 50 hours" what at the end?

Q. 30 to 50 hours of work that you previously estimated?

CERTIFIED STENOGRAPHER: That's correct you said?

A. Yes, that's my estimate.

BY ATTORNEY BROWN-MARSHALL:

Q. What is your hourly rate for this case?

A. So as I detail I think in my -- as I know in my declaration, my rate is $800 an hour.

Q. Do you do any consulting work aside

from the legal work that you've done on this matter and the other patent matter that you're working on?

A. Yes, I do.

Q. Okay. And what is your hourly rate for the consulting work that you do?

A. So I would say it varies between around 650 to a thousand dollars an hour, but in that range, depending on the nature of the work.

Q. So of that 30 to 50 hours, approximately, that you've worked on this case, how much of that was spent preparing your declaration?

A. So in essence, everything I did up to the submission of my declaration was part of preparing for my declaration, because I was reviewing all of the important documents from the case, including the declarations of others, the patent, the prior art, and so I would say the majority of that time has been dedicated to preparing background information and then actually compiling my declaration.

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?

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.

- - -

(Whereupon, document entitled

Rebuttal Declaration of Paul E. Oberstein, M.D., is received and marked as Exhibit 1150 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 1150.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, your declaration, Exhibit 1150, includes a list of materials considered; correct?

A. Which list are you referring to?

Q. So there is a list of materials considered in your declaration; correct?

A. I'm sorry, my question was: Which list are you referring to?

Q. I'm referring to the list of materials considered.

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

A. Perhaps you can clarify where in the declaration you're referring to?

Q. So if you go to Page 8, just above Paragraph 18, there is a section header called: Materials considered.

A. Yes, I'm there.

Q. Okay. And this is a list of the materials that you considered in formulating your opinions that are contained in this declaration; correct?

A. That is correct.

Q. And that list also includes the documents that are listed in Appendix A; is that correct?

A. That is correct.

Q. With the correction that you were removing Exhibits 1135 and 1137; correct?

A. That is correct.

Q. So the materials that are listed in this materials considered section at Paragraphs 18 and 19, and materials listed in Appendix A, are those all the materials you reviewed in coming to your opinions in this case?

A. So the materials listed in the -- as you said, in Page 8 or Paragraph 18, Section 4, and the materials in the appendix were the information that I utilized to evaluate the case and to evaluate the '393

patent from the perspective of the person of ordinary skill, and enabled me to come to the conclusion that each and every claim limitation in the patent is included in the prior art.

They were sufficient for me to make that conclusion. There were other sources that may have come across my awareness during the preparation, but I was able to make that conclusion based on the material I described here.

Q. But you didn't list those other resources that came across your awareness; correct?

A. So I listed resources that I felt were necessary for me to come to the conclusion that I described in the beginning of my declaration, that each and every claim limitation of the '393 patent is included in the MSI study record and the prior art.

Q. What other materials did you consider that you didn't list in your materials considered in your declaration?

A. So I don't have specific examples.

As part of my independent research, to come to my conclusions, I looked at many manuscripts, and there were certainly some that I looked at that were not included here, that I think did not add to the strength -- were not necessary for me to make that conclusion.

Q. So you're not relying on any of those additional manuscripts to support the opinions in your declaration?

A. That is correct.

Q. In your work in this case, did you review any memos or depositions or documents related to the case that are not listed in this materials considered section?

A. So as I stated -- you mean -- I'm sorry, can you clarify the question?

Q. So you previously spoke about references that you reviewed that are not listed in the materials considered section. Did you review any case-related materials that are not listed in the materials considered section?

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

A. As I stated earlier, I did review Dr. Neugut's deposition, which is not listed in this list of materials considered. As I stated, it did not change my conclusion in this case about the underlying conclusion of my declaration.

Q. Did you review the petition that Merck filed in this case?

A. Which petition?

Q. So you understand that this is an IPR proceeding which starts with a petition that is filed by the petitioner?

A. Yes.

Q. Okay. Did you review Merck's petition in this case?

A. Do you have that petition for me to refresh my memory?

Q. No, I don't. I'm just wondering if you reviewed it?

A. I don't recall specifically if I reviewed it or not.

Q. Okay. Did you review any of the responses that Johns Hopkins has filed in this case?

A. Again, can you tell me how many responses there were or --

Q. There is two responses. There is a preliminary response and then there is a patent owner's response. Did you review any, either of those responses?

A. So I certainly recall reviewing the patent owner response, POR.

Q. Uh-huh.

A. I don't recall if I reviewed the other one or if it was available to me.

Q. Okay. But you didn't list Johns Hopkins patent owner's response in your list of materials considered?

A. That's correct, because as I said, the materials considered, the ones that I thought were essential in me forming my primary conclusion, which is that each and every claim limitation in the '393 patent is included in the prior art, specifically in MSI study record with other prior art, and I did not think that was necessary or changed my conclusion.

Q. In your work in this case, were you

shown any other docs other than those listed on your list of materials considered?

A. So as I just stated, I definitely recall seeing the patent owner response, as well as some other filings in front of the Patent Office.

Q. Okay. What other filings were those?

A. I don't recall the exact specifics of any other filings in front of the Patent Office.

Q. So aside from filings of the Patent Office, were you shown any other documents, other than those in your materials considered list, in your course of your work in this case?

A. And when you say "shown," what do you mean by that?

Q. Did Merck or its attorneys provide you with any additional documents?

A. I do not recall Merck or its attorneys providing me any documents besides those listed in the materials considered and 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.

A. I'm sorry, these are the exhibits that I relied on to prepare my declaration.

Q. Let me ask this a different way.

What is the source of the documents that are listed in Appendix A?

A. I don't understand the question.

Q. How did you identify the documents that you reviewed that are listed in Appendix A?

A. Again, I -- I looked at the documents that I used in preparation of my declaration.

Q. How did you decide to look at those documents?

A. Some of them were primary documents that I found. Some were provided to me by counsel. Some were referenced in other people's declarations or depositions.

Q. Do you have a copy of Dr. Neugut's declaration?

A. I do.

Q. Okay. Could you open that up?

ATTORNEY BROWN-MARSHALL: So this is Exhibit 1003.

- - -

(Whereupon, document entitled Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H., is received and marked as Exhibit 1003 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 1003.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, are you familiar with Exhibit 1003?

A. I did review Exhibit 1003, Dr. Neugut's declaration.

Q. Okay. If you would turn to the back pages starting on Page 90. I'm sorry, yes, Page 90 of 97. And if you would -- so do you see on Page 90 where it says: Appendix A, and then it gives a list of exhibits?

A. Yes.

Q. Okay. And these are the exhibits that Dr. Neugut relied on in formulating his opinion?

A. That is my understanding of Appendix A and Dr. Neugut's declaration.

Q. Okay. If you would quickly compare

Appendix A in Dr. Neugut's declaration to Appendix A in your declaration and let me know if they're the same.

A. So I'd rather not do that quickly. You want to take the time to go to each one?

Q. Well, the exhibits are numbered; correct?

A. Correct, there is over 100 exhibits.

Q. So Dr. Neugut's declaration starts with Exhibit 101, which is the '393 patent; correct?

A. That is correct.

Q. Okay. And you understand that in an IPR proceeding, that exhibits maintain their exhibit numbers throughout the proceeding?

A. Yes.

ATTORNEY RATLIFF: Go ahead.

Q. Okay. So if Exhibit 1001 in Dr. Neugut's declaration is the same as Exhibit 1001 in your declaration.

ATTORNEY RATLIFF: If that's a question, I object to the form of the

question.

A. I'm just trying to clarify. Do you want me to go through one by one and confirm that each exhibit is either the same or not the same between the two declarations?

Q. I don't know if it's necessary to go all the way through, but your Appendix A, you rely on Exhibits 1001 through 1148; correct?

A. That is correct.

Q. Okay. And Dr. Neugut's declaration, he also relies on Exhibits 1001 through 1084; is that correct?

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

A. That is correct. Those are different numbers you're just saying?

Q. So both you and Dr. Neugut rely on Exhibits 1001 through 1084; correct?

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

A. So I would need some time to go through each exhibit to say whether that's

true. We both do quote Exhibit 1001 and Exhibit 1084, if that is your question.

Q. So your Exhibit A includes the materials that Dr. Neugut relied on in formulating his declaration, the opinions in his declaration; correct?

A. So in my declaration, I utilize many of the same materials Dr. Neugut utilized. Again, without going through each exhibit one at a time, I can't clarify -- I can't confirm whether there are any materials in Dr. Neugut's declaration that are not referenced in mine, and I know vice versa there certainly are.

Q. Did you review all of the references that Dr. Neugut relied on in formulating his opinions?

A. I reviewed the references that Dr. Neugut utilized in forming his opinions, yes.

Q. Okay. And you included those on your materials considered?

A. As I said before, included information in my materials considered if I

thought it was helpful and important for me to establish my primary conclusion, which is that each and every claim limitation of the '393 patent was included in the MSI study record and available material at the critical date of July 10 of 2015.

Q. Dr. Oberstein, I didn't ask you about your conclusions. I asked you about your materials considered.

ATTORNEY RATLIFF: If that's a question, I object to the form of the question.

A. So my materials considered were the materials I considered in formulating my conclusion, so I included the things that I thought were important to justify and to support my primary conclusion.

Q. Are there any materials that Dr. Neugut relied on that you decided not to include in your materials considered list?

A. I don't recall any specific examples, but again, I would have to review everything he relied on and the appendix to tell you whether or not there are any specific

examples.

Q. So in your declaration, you note numerous opinions of Dr. Neugut that you agree with; correct?

A. There certainly are many things that I agree with Dr. Neugut and quote in my declaration, yes.

Q. And I counted those up and there are over 75 instances in your declaration where you note that you agreed with Dr. Neugut; correct?

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

A. So you're asking if your count is correct? I did not count them up.

Q. Does that sound like a reasonable ballpark?

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

A. So I don't have a reasonable ballpark. I could state that I agree with Dr. Neugut on many points and quote him in that context when I agree in my declaration.

Q. All right.

Were there any opinions from Dr. Neugut that you disagreed with?

A. So I didn't evaluate Dr. Neugut's declaration with an eye to agreeing or disagreeing with what he stated.

My role here as an independent expert was to evaluate the '393 patent, and from a person of ordinary skill at the critical date of July 10, 2015, I evaluated that each and every claim limitation in that patent was previously taught in the prior art, including the MSI study record. That is what I described in my declaration and what I went out to do. I don't have specific rebuttal or comments on Dr. Neugut's declaration.

Q. But there is no instances in your mind of issues or opinions that Dr. Neugut provided that you didn't agree with?

A. I cannot agree with that statement without giving it more serious thought and going through his declaration with that question in mind. That was not the task I sought after in this expert testimony.

Q. So how did you decide which

opinions of Dr. Neugut's that you agreed with?

A. So I evaluated -- I read Dr. Neugut's declaration, carefully evaluated points he raised and sources that he brought, and I included the things that I felt were important for me and important for the conclusion that I came to in this declaration.

Q. So you evaluated each of Dr. Neugut's opinions?

A. So I evaluated all of the information in light of the goal that I -- the goal that I had, which was to give an independent review of the '393 patent in light of prior art.

Q. But you identified over 75 instances where you agreed with Dr. Neugut; correct?

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

A. I don't have a specific number, but as I said, there are many instances in which I agree with Dr. Neugut, as I stated in the declaration.

Q. So you evaluated his opinions. You

identified many opinions of Dr. Neugut's with which you agreed, but you didn't identify any opinions from Dr. Neugut with which you disagreed?

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

A. So I did not say that and I do not agree with your statement. I specifically wrote in my declaration the points that I agreed with. I did not make any listing anywhere of things I didn't agree with or compile such a list.

Q. I understand that you didn't make a listing of it, but I'm asking: As part of your objective evaluation where you looked at Dr. Neugut's opinions, you identified ones that you agreed with, but you didn't identify any that you disagreed with?

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

A. So, again, what I laid out here and what I tried to be very clear about was the

specific objective of evaluating the prior art and the '393 patent, coming to a conclusion of what a person of ordinary skill as of the critical date of July 10, 2015 would have concluded, and my conclusion is that each and every claim limitation in the '393 patent is included in the MSI study record and prior art.

That is what I am comfortable describing in my declaration, and that's where I utilized Dr. Neugut for points where I agreed with him about my findings and where he stated it in a similar fashion.

Q. So you cherry-picked the opinions of Dr. Neugut that aligned with your opinion?

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

A. So, again, I conducted an independent review as an outside expert how a person of ordinary skill in the arts would have evaluated the prior art at the time of July 10, 2015, and where Dr. Neugut's opinion was similar or concurrent with what I concluded, I quoted Dr. Neugut affirmatively.

Q. So you didn't bother evaluating Dr. Neugut's declaration for opinions that you disagreed with?

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

A. So I do not agree with that. I evaluated Dr. Neugut's declaration completely, but in my declaration, I sought out to provide expert testimony about the specific question in front of me.

Q. I guess what I'm not understanding is how do you objectively evaluate the opinions of another and only identify opinions that you agree with?

ATTORNEY RATLIFF: If that's a question, I object to the form of the question and to the premise of the question.

A. So I didn't testify in my declaration about items that I disagreed with in my evaluation with any sort of comprehensiveness. I testified specifically about the role of a person of ordinary skill in evaluating available prior art, including

the MSI study record and finding taught in that prior art each and every claim limitation of the '393 patent.

Q. I didn't ask about formulating your opinion. I'm asking about your assessment of Dr. Neugut's opinions, and you said that you made an objective assessment, correct, of Dr. Neugut's opinions?

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

A. So in my declaration, I do not give an overall objective assessment about Dr. Neugut or anybody else for that matter. I point out areas in which other findings support or build my conclusion that I came to and those are the things I quote.

Q. I'm not asking about your declaration. I'm asking about your assessment of Dr. Neugut's preparation, and you said that you made an objective assessment of his opinions; correct?

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

A. So prior to including any item in which I quote agreeing with Dr. Neugut, I made an objective assessment as to whether I agreed with that opinion. It does not say what I think about other things in Dr. Neugut's declaration or anybody else's declaration if I didn't specifically discuss them in my own declaration.

Q. But I'm asking: When you made that assessment, did you identify any opinions in Dr. Neugut's declaration of which you disagreed?

A. So I don't recall any specific examples, but there were many things in Dr. Neugut's declaration that I did not quote or utilize in my own declaration, and so there may be other things that I disagreed with in that declaration. I do not -- again, as I said, my role here was not to compile those or critically list them, and I did not do that in my declaration.

Q. So sitting here today, you cannot identify any opinions in Dr. Neugut's declaration with which you disagree?

A. So off the top of my head, I don't have any specific examples, and I did not prepare those for my declaration.

Q. So you can't identify them sitting here today?

A. I want to be very clear. There may be things there. I can't specifically identify any items right now in which I don't agree with Dr. Neugut in his declaration.

Q. So, Dr. Oberstein, one of the other exhibits that you've listed on your materials considered is the declaration of Dr. Nils Lonberg; correct?

A. That is correct.

Q. And did you review Dr. Lonberg's declaration?

A. So I did review Dr. Lonberg's declaration.

Q. And in your declaration, you include several opinions from Dr. Lonberg of which you disagree; correct?

A. That is correct.

Q. And did you review any of the exhibits cited by Dr. Lonberg?

A. I did review some of the exhibits cited by Dr. Lonberg, yes.

Q. Okay. Which exhibits cited by Dr. Lonberg did you review?

A. So I cannot recall exactly examples at this time, but in reviewing Dr. Lonberg's declaration, and there was an exhibit that I wanted to understand what he was bringing from that exhibit, I would have looked up that exhibit and I did that.

Q. But you didn't include those on your materials considered list?

ATTORNEY RATLIFF: Are you representing that to him or is that a question?

Q. Did you include any of the exhibits cited by Dr. Lonberg that you ostensibly reviewed in your materials considered list?

A. So I did include in my materials reviewed several references that were also quoted by Dr. Lonberg, for example, the MSI study record or the '393 patent, as well as many of these other references I talked about earlier.

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

letter two or the letter one and whether he was quoting things that have previously been referenced.

Q. Do you understand that Dr. Lonberg cited exhibits that were not included in the Neugut declaration?

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

A. Yes, I understand that.

Q. Okay. And did you review any of those exhibits that weren't cited by Dr. Neugut in his declaration?

A. So I can't recall specifically, but I believe that I did, because I reviewed, as I said, Dr. Lonberg's exhibits to look at what he was quoting from those exhibits, and many of those may -- well, some of them may not have been included in Dr. Neugut's declaration.

Q. How many exhibits cited by Dr. Lonberg did you review?

A. I do not specifically recall.

Q. But 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. 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.

A. So as I understood it, my

assignment in this case was to be an independent expert, to evaluate the information in the '393 patent in light of the prior art for a person of ordinary skill. I did that unbiased, open-minded evaluation of all the information that was available to me and that I could discover, and my conclusion, which I outline here, is that each and every claim limitation of the '393 patent was included in the MSI study record and other prior art at the critical date of July 10, 2015, and would have been taught that way to a person of ordinary skill.

That's -- I included everything in my declaration that supported me making that conclusion. I did not include specific critiques outside of my conclusion of other experts in this case.

Q. So you did not address the other references that Dr. Lonberg cited in support of his opinions with which you disagree?

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

A. So I cited references to support

the opinion that I took in this declaration and included everything that I thought was important to support and to back up that convention that I came to in this declaration.

Q. But you didn't address any of the pieces of evidence that Dr. Lonberg cited as being contrary to those opinions; correct?

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

A. So, again, I specifically looked at this as an independent and open-minded evaluation of the '393 patent and the prior art. I did not specifically go down other people's points and give a rebuttal or counterargument to those points. I looked at this independently utilizing the prior art, and I did review Dr. Lonberg's arguments in his declaration and came to the conclusions that I outline in this declaration.

Q. So you say that you didn't specifically go down other people's points and give a rebuttal or counterargument to those points, but you did express the opinion that

you disagree with Dr. Lonberg's points; correct?

A. So in some parts I noted that I disagreed where it was important and summarized my opinion in the case. I also noted some areas where I did agree with Dr. Lonberg. That's not a comprehensive list of every assessment of every statement of Dr. Lonberg.

Q. But for those points where you said that you disagreed, you did not directly address the evidence that Dr. Lonberg relies on in support of his opinions with which you disagree?

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

A. So I specifically explained why I disagreed with Dr. Lonberg and what the points of evidence were that supported my conclusion that Dr. Lonberg is incorrect in the parts that I disagreed with him. I quoted primary sources, specifically the MSI study record, to support the conclusion that I made that each

and every claim limitation of the '393 patent was previously taught in the MSI study record in prior art and would have been appreciated by a person of ordinary skill as of the critical date.

Q. But in doing so, you did not evaluate any of the counterevidence that Dr. Lonberg 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.

A. What do you mean by "evaluate"?

Q. Well, in your declaration, you don't cite to any of the evidence that Dr. Lonberg cites in support of his declaration; correct?

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

A. So in the summary at least and in more detail where I disagree with Dr. Lonberg about specific points, I explain why I disagree and why I take the opinion that I came to in this declaration.

Q. And the support for that, for those

opinions where you explained why you disagree and why you take the opinion that you came to, those are based on materials that are listed in your materials considered list; correct?

A. Correct, and those are similar materials to those that Dr. Lonberg quoted.

Q. But they don't include the additional evidence that Dr. Lonberg identified in his declaration; correct?

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

A. So I don't specifically quote Dr. Lonberg's arguments in every regard.

Q. That wasn't my question.

In your declaration, you do not address the additional evidence that Dr. Lonberg identified in his declaration; correct?

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

A. So in my initial description of my overall findings, I only quote the primary

source, which is the -- the primary source of my findings, which is the MSI study record, which is the same source that Dr. Lonberg utilized in his declaration and disagree with him in that regard.

Q. But the additional evidence that Dr. Lonberg cited in support of his opinions, with the exhibits that Johns Hopkins submitted, you don't rely on any of that evidence in support of your opinions in your declaration; correct?

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

A. So I utilized the information that I think is absolutely essential to make the conclusion that I concluded in this declaration and quote what I think is necessary to come to that conclusion. I didn't quote anything else that I thought was not necessary for that conclusion.

Q. So you evaluated the exhibits submitted by Johns Hopkins on which Dr. Lonberg replies and you determined that

they were nonessential?

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

A. What do you mean by "nonessential"?

Q. Well, you just said that "the information that I think is absolutely essential to make the conclusion that I concluded in this declaration." So you determined that some exhibits and evidence were essential and some were nonessential?

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

A. So I approached this as an independent expert and looked at the prior art, as well as the other information available to me, and my conclusion from reviewing the prior art was that a person of ordinary skill, as of the critical date of July 10, 2015, would have found information and been taught by the prior art that each and every claim limitation of the '393 patent was previously taught, specifically in the MSI study record and supporting documentation as I

quote. Those are the references that I then put into my declaration to support that conclusion.

Q. So, Dr. Oberstein, what do you mean when you use the term "prior art"?

A. So generally, by prior art, I refer to information that was public and published and available to a person of ordinary skill at the time of the critical date of the patent, which in this case I utilized July 10, 2015.

Q. And what specific pieces of prior art are you relying on for your opinions contained in your declaration?

A. So I have a pretty extensive list of what I'm relying on, which includes the materials considered, but of those, I specifically in my declaration review several, I call, key elements, because I quote them in detail, but there are, of course, more, and those include the MSI study record, as well as the six articles that I previously referenced, which I can give you the names if you'd like.

Q. That's all right. We've already been through those.

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

Merck's counsel?

ATTORNEY RATLIFF: He didn't say allege. I object to the form of the question.

A. I'm sorry, can you repeat the question?

Q. So you identified Exhibit 1148 as a reference of what you allege is prior art that you identified independent of the list that Merck's counsel gave you; correct?

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

A. That is correct.

Q. Okay. Are there any other pieces of alleged prior art that you identified that you relied on in forming your opinions in your declaration, other than Exhibit 1148?

A. So as part of my independent evaluation for this matter, I certainly identified other prior art that was not included in the list that Merck had provided for me. I did not, as far as I recall, feel that any of those would need to be included to derive the conclusions that I wanted to present or that came up with to present in

this declaration.

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

So you didn't rely on any other additional pieces of alleged prior art that you've identified in formulating your opinions that are contained in your declaration?

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

A. So I'm not sure if we're saying the same thing, but I would say that the prior art references that I refer to in my declaration were sufficient to justify the conclusion that I came to, that a person with ordinary skill in the art would have found that all the claims of the '393 patent are taught or suggested in the MSI study record, and the prior art references that I quoted, I did not feel that I needed to add any more references to justify and explain that conclusion.

Q. And those were the same conclusions that Dr. Neugut reached; correct?

A. So there are many similarities 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

something that was similar to what I wanted to write, I referenced his statement of that.

Q. So your independent opinion just happens to rely on the same list of prior art that Dr. Neugut relied upon; correct?

A. So my independent opinion came from a review of the prior art. It also reviewed, as I describe here, many declarations and depositions and other pieces of information, and my conclusion from that prior art was that each and every claim limitation of the '393 patent was previously taught and would have been appreciated by a person of ordinary skill as of July 10 of 2015.

ATTORNEY RATLIFF: And, counsel, we've been going over for an hour, so let's take a break.

THE WITNESS: That would be great.

ATTORNEY BROWN-MARSHALL: Okay.

CERTIFIED STENOGRAPHER: Off the stenographic record at 9:04 a.m.

- - -

(Whereupon, a short recess was taken.)

- - -

CERTIFIED STENOGRAPHER: Back on the stenographic record at 9:16 a.m.

BY ATTORNEY RATLIFF:

Q. Dr. Oberstein, did you review the declaration of Dr. Richard Goldberg?

A. Yes, I did.

Q. And did you review any of the exhibits cited by Dr. Goldberg, and for the record, what are you looking at, Dr. Oberstein?

A. Dr. Goldberg's declaration.

Q. And that is Exhibit Number -- it should be in the corner?

A. 2090. Yes, I did look at some of the references that Dr. Goldberg quoted.

Q. Okay. Which ones?

A. I don't recall specifically right now. It's quite some time ago when I reviewed this, and as I said, when I saw something that I wanted to clarify, I looked it up.

Q. Okay. But you don't list any of those exhibits on your materials considered; correct?

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

A. So some of those exhibits are overlapped with what I quoted. I'm sorry, I don't understand the question.

Q. Okay. Which of Dr. Goldberg's exhibits are you relying on in formulating the opinions in your declaration?

A. So I relied on the exhibits that I referenced in my declaration to formulate the opinion in my declaration. Where Dr. Goldberg quotes the same exhibits, we share those exhibits.

Q. Okay. So you're not relying on any new exhibits identified by Dr. Goldberg in his declaration?

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

A. So I only included the exhibits that I thought were -- that I relied on to come to my conclusion in my declaration. I didn't include anything else that came from other sources that I did not think were necessary to explain and justify my

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?

A. That exhibit was something that I reviewed in the summary after Merck reached out to me about representation in this case. I don't recall if I saw that exhibit prior, in the course of my regular research in clinical activities.

Q. And you also rely on the Pernot exhibits, Exhibit 1006; correct?

A. That is correct.

Q. Okay. When was the first time that you saw the Pernot exhibit?

A. Again, I know that I was made aware of that exhibit after I engaged with Merck about performing an evaluation for this case. I don't recall if 10 years ago or 15 years ago I saw that exhibit as well.

Q. So you have no recollection of encountering the Pernot exhibit prior to your work on this case?

A. I have no specific recollection. I look at many articles over the course of time and it was over a decade ago, so I can't say I specifically recall it, but there is a chance 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

outreach and attending the lecture by Dr. de la Chapelle, did you have any other contact with him while you were at Ohio State?

A. Not that I recall.

Q. You also rely on the Steinert exhibit, which is Exhibit 1008?

A. That is correct.

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

A. So as I recall, the first time I read that was the summer after I was engaged to evaluate this case.

Q. And you also rely on the Salipante exhibit, which is Exhibit 1009 -- oh, no, sorry. Correct that. You also rely on the Salipante exhibit, which is Exhibit 1010; correct?

A. I have to confirm the numbers. That is correct.

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

A. Again, I don't recall specifically having read it prior to engaging in this 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

thoroughly. There are some others that were -- potentially I looked at the critical elements that were quoted by other people in the case to verify that it was there and that it was the right context, but I can't say that I reviewed them in detail or can recall all the specific details.

Q. And in addition to the references listed in your materials considered, you also looked at some of the references cited by Dr. Lonberg and Dr. Goldberg; correct?

A. That is correct.

Q. Okay. How many hours did you spend reviewing references that are -- strike that.

How many hours did you spend reviewing references in total for this case?

A. So I can't recall a specific number of hours. I think pertinent to your earlier questions about how many hours I spent in review, as I review all of this, I think the -- I have to tally up all the hours. I spent quite a considerable amount of time in reviewing records.

Q. But it's not more than 30 to 50

hours; correct?

A. So I -- I -- I think I have to clarify and go through and count up the exact time. I can't give you an exact number of time based on the fact that I haven't tallied that up yet.

Q. But it was your testimony that your total hours spent on this case is 30 to -- approximately 30 to 50 hours; correct?

A. Correct.

Q. Okay. So the number of hours that you spent reviewing can't be more than the total number of hours; correct?

A. Correct. So that was an approximate number, and I think that as I go up and tally my numbers, it certainly may change.

Q. Do you know how many pages are included in all the references you've listed in your materials considered?

A. I do not know how many pages.

Q. So we added it up and it's over 7600 pages of references.

ATTORNEY RATLIFF: If that's a

question, I object to the form of the question.

Q. So you reviewed over 7600 pages of references in less than 30 to 50 hours; correct?

ATTORNEY RATLIFF: So now it sounded like a representation. So I object to that representation, and I'll object to the form of the question.

A. So I would not say that. I think that I did keep -- did review all the information that I said I reviewed or I described as reviewing, and I have to count up the hours, and it may turn out that it was more than I anticipated of 30 to 50 hours.

Q. But that 30 to 50 hours, even if it's more, also includes the time that you spent working on drafting your declaration; correct?

A. That is correct. As I said, reviewing these records had a critical role in my mindset in drafting my declaration.

Q. And even though they played a critical role, you still spent less than 30 to

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. 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.

Q. And which of your materials

considered were identified by that literature search that you performed?

A. So I essentially found additional references that I thought were relevant, but none of them were necessary, in addition to what I described here, to justify and come to the conclusion that I came to that the prior art as of July 10, 2015 described each and every claim limitation in the '393 patent, including specifically the MSI study record and other prior art.

Q. So you don't rely on any additional articles you identified via a literature search in formulating your opinions in your declaration?

A. I rely just on the articles that were laid out here in materials considered.

Q. And none of those were articles that you identified via a literature search?

A. I gave you one example prior of something in Appendix A that I identified through a search of a clinical trial record, but outside of that, these were not ones that I independently identified through a

literature search.

Q. And, Dr. Oberstein, you're not relying on any regulatory filings from Merck with the FDA in formulating your opinions in your declaration; correct?

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

A. What do you mean by "regulatory filings"?

Q. So you understand that pharmaceutical companies need approval from FDA to sell a product; correct?

A. Pharmaceutical companies?

Q. Yes.

A. That is correct.

Q. Okay. And you understand that Merck has approval from FDA to sell Keytruda; correct?

A. That is correct.

Q. Okay. Did you review any regulatory -- sorry. Strike that.

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 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

conference, so there were several other people on the line. I know some of them I recognize from this team at Paul Hastings. I can't give you every name. Dr. Sheridan, and I don't know if there were other people from Dr. Sheridan's team on the call.

Q. And what was discussed on that first conversation with Dr. Sheridan?

A. So as I recall, Dr. Sheridan asked me for background information about the diagnosis, staging, and treatment of colon cancer, as well as the way MSI-high colon cancer might be diagnosed and the treatment that you would utilize in that setting, including immunotherapy, such as pembrolizumab.

Q. Anything else discussed on that first call?

A. So we had a lengthy conversation. I don't recall every single detail. I have some recollection that we discussed some of the percentages of different staging, meaning what percentage of patients have Stage 1, Stage 2, and things of that nature, which is

relevant, of course, for the treatment described.

I also -- I had a second conversation with Dr. Sheridan where I know it was right before I submitted my declaration and reviewed with him some of the conclusions that I had made in my declaration. I don't know if I gave him any of that preliminary information in the first call.

Q. So you said that the first call was lengthy. Approximately how long did it last?

A. I'd say 30 to 40 minutes.

Q. And you said the second conversation with Dr. Sheridan occurred -- was it the day that you signed your declaration?

A. It was certainly not the day I signed it, but it was, I think, that week.

Q. Okay.

A. So I submitted my declaration on a Friday. It was some day earlier in that week, if I recall correctly.

Q. Okay. And who attended that second conversation with Dr. Sheridan?

A. So a very similar cast of

characters, attorneys that I know from Paul Hastings, and again, I don't know if there were attorneys from Merck on that call, and Dr. Sheridan, of course.

Q. And what was discussed on that second conversation?

A. So Dr. Sheridan had some follow-up questions for me, which I recall had more to do with the specific utilization of immunotherapy, such as pembrolizumab or nivolumab for MSI-high colon cancer patients, and I reviewed with him some of my understanding if -- the MSI study record and how in my opinion to a person of ordinary skill in the art an MSI study record anticipated and taught each and every claim of the '393 patent.

Q. Did you and Dr. Sheridan discuss anything else on that second call?

A. It's very possible. I don't recall every single detail that we discussed.

Q. Approximately how long did that second call with Dr. Sheridan last?

A. As I recall, it was also around 30

minutes. Slightly shorter maybe.

Q. And have you spoken with Dr. Neugut in conjunction with this case?

A. I have not.

Q. Do you have an understanding of why you were asked to put in a declaration responding to Johns Hopkins' patent owner response instead of Dr. Neugut?

A. I do not.

Q. Have you had any conversations with Ross Pierce in conjunction with this case?

A. What is Ross Pierce?

Q. He was a potential expert identified by Merck.

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

A. I don't think so.

Q. The name doesn't ring a bell?

A. No.

Q. Okay.

A. But I already said names are not the best, but I do not recall that name or a conversation with anyone outside of this counsel about this case.

Q. And did you have a conversation with John Bone in conjunction with this case?

A. John who?

Q. Bone, B-O-N-E.

A. I don't think so.

Q. So other than Dr. Sheridan, have you spoken with anyone else in conjunction with this case?

A. I do not recall speaking to anyone outside of the legal team from Merck and Paul Hastings, who are here, and their colleagues.

Q. What did you do to prepare for this deposition today?

A. I got a good night's sleep. I read over my declaration and skimmed, as you pointed out by the many pages, some of the other pieces of prior reference and sources that I quote in my declaration.

Q. Did you meet with counsel?

A. And I met with counsel and reviewed some of that.

Q. How many times did you meet with counsel?

A. Overall or specifically in this

context?

Q. In preparation for the deposition today?

A. I think we met four times.

Q. Four times? Okay.

When was that first meeting with counsel?

A. Friday of this past week I believe.

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

A. Approximately two hours.

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

A. So that was a Zoom as well. So the attorneys from Paul Hastings here were present there and I think that was it.

Q. And when did the second meeting with counsel in preparation for this deposition occur?

A. The second meeting was this past Sunday.

Q. Okay. And --

A. Do you need the date or no? I don't remember the date, but what's today?

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.

Q. Okay. So you had the basic course of immunology in medical school.

After medical school, did you receive any instruction or training in immunology?

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

A. So, yes, during my fellowship, I did a subsequent fellowship in clinical trial design and patient-oriented research. I took graduate-level classes in immunology at Columbia.

Q. At Columbia.

Do you have any training in cancer genomics?

A. I have basic training in cancer genomics as part of medical school and my fellowship training, but I don't have any advanced training in cancer genomics.

Q. What did the training in immunology that you received during your fellowship entail?

A. Graduate-level classes and subject

matters about immunology, specifically immunology of cancer.

Q. And you're currently employed as the service chief in the GI oncology practice with the Perlmutter Cancer Center at NYU Langone Health; correct?

A. That is correct.

Q. Did you audition for their Super Bowl commercial?

A. On the record, I did not.

Q. Okay.

A. But I was featured in a separate commercial that we're hoping will run soon, where they got a lot of pushback, so I don't know what's going to happen.

Q. Okay. We'll have to keep an eye out.

A. So watch out for me.

Q. Okay. How long have you been employed by NYU Langone Health?

A. Seven years. I think March 1 is my anniversary, so it will be seven years on March 1.

Q. And which years? What years does

that span?

A. March 1, 2018 to today.

Q. And you are currently a practicing medical oncologist focused on GI cancers, especially colorectal, pancreatic, and gastric cancers; correct?

A. That's correct.

Q. When did you first begin treating cancer patients?

A. So in, I would say, July of 2010 is when I started treating cancer patients.

Q. And that was when you began your fellowship in oncology?

A. That's correct.

Q. And when did you start focusing on GI cancer patients?

A. So actually, I would say within six months of that time. Most fellowships, including the one I did, consist of a small -- not a small, but a period of time of clinical knowledge and expertise and research time, and so my research time, which I started within six months of starting fellowship, was focused on GI cancers, and that's where it became my

focus.

Q. And do you treat your GI cancer patients with immune checkpoint inhibitors?

A. When it's appropriate, absolutely.

Q. And which immune checkpoint inhibitors do you prescribe to your patients?

A. So I currently prescribe several FDA approved immune checkpoint inhibitors, and I also engage in clinical trials where we use many checkpoint inhibitors that are not FDA approved or not yet FDA approved.

Q. Okay. So let's put aside the clinical trials for a minute, and just talking about the FDA approved immune checkpoint inhibitors that you prescribe.

Which specific ones do you prescribe to your GI cancer patients?

A. You'd like a list?

Q. Sure.

A. Nivolumab and ipilimumab; pembrolizumab; dostarlimab. Those are medication, I don't remember the current name, but tremelimumab. There is a drug that I think used to be called MD4736 that now has

been approved and has a brand name. I don't recall the brand name, but those are the ones that I recall off the top of my head. There probably are more.

Q. And do you prescribe the same immune checkpoint inhibitors to, let's say, a gastric cancer patient as you would prescribe to a pancreatic cancer patient?

A. So sometimes we do and sometimes we don't. It depends on why we're giving the immune checkpoint inhibitors, what the indication is, what features of that person are, and what the FDA approval is.

Q. So when you prescribe an immune checkpoint inhibitor to one of your GI cancer patients, you prescribe those under an indication that is listed on the label of the drug; correct?

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

A. So not necessarily. We often do, but there are times we use medications, quote/unquote, off-label.

Q. And when would you use an immune

checkpoint inhibitor off-label with one of your GI cancer patients?

A. So there may be an instance where one is concerned that an approved immunotherapy has side effects that are intolerable and that another immunotherapy might be more tolerable, and we would use that instead or based on insurance issues, sometimes where an insurance company will approve one and not the other. There could be other factors as well.

Let's say treating patients, you know, is quite dependent on the individual patient and the individual circumstances.

Q. When did you first start prescribing immune checkpoint inhibitors for your GI cancer patients?

A. So I don't have an exact recollection of when I first prescribed the medication. I can't say more than that.

Q. Do you remember was it during your fellowship?

A. I don't recall -- I recall 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.

Q. And prior to 2015, were you

involved in any clinical trials related to pembrolizumab?

A. So I don't recall exactly when, but I know that as soon as pembrolizumab obtained its first approval in melanoma, its use became quite widespread in clinical trials, and I was definitely involved in clinical trials at that point. I don't have the specific dates for when they started. I think -- I know it was around that time period since the approval came prior to 2015.

Q. And do you remember which types of cancer were involved in those pembrolizumab clinical trials that you participated in?

A. So I don't recall exactly. I only treat GI cancer, so it was certainly one of those, but I can't recall the exact studies I was involved in at that time period.

Q. Okay. Were you -- prior to 2015, were you involved in any clinical trials related to treating MSI-high cancer with pembrolizumab?

A. I don't specifically recall if any of the trials I was involved in had specific

cohorts for MSI-high patients.

I certainly treated colon cancer patients in clinical trials, and they would have been included if the trial wrote it that way, but I don't have a specific recollection.

Q. And when you say that you treated colon cancer patients in clinical trials, do you remember which drug was involved in those clinical trials?

A. So, again, I don't have the final dates I would say in my head. I know I was involved in a colon cancer trial that would have been a drug called Celecoxib around that time period, and the question was whether that has utilization for colon cancer patients, but I don't recall their specifics.

Q. Prior to 2015, were you involved in any clinical trials relating to the use of pembrolizumab in colon cancer patients?

A. So as I said before, I don't recall. It's possible, but I can't recall specifics.

Q. Have you been involved with any clinical trials related to the use of

pembrolizumab in treating colorectal cancer patients since 2015?

A. I don't recall specifically.

Q. Okay. But you have been involved in clinical trials involving the use of pembrolizumab to treat GI cancers; correct?

A. Absolutely.

Q. Okay. Which GI cancers?

A. So I could speak to the trials that I wrote, which I'll try to remember well, but I -- in 2016, I started a clinical trial, wrote and designed a clinical trial utilizing pembrolizumab for the treatment of gastric cancer, stomach cancer.

I've also written studies in pancreatic cancer, and I've certainly -- with pembrolizumab and been involved in other studies with pembrolizumab both in stomach cancer, liver cancer, and something called cholangiocarcinoma or bile duct cancer.

Q. And when you say that you wrote a clinical trial, what do you mean by that?

A. I mean, that I collaborated with the team to -- I serve as a principal

investigator and thus collaborated with the team to design, write, and submit a clinical trial for approval.

Q. What's involved in writing a clinical trial?

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

A. That is a very broad question.

Q. Okay. Just at a high level.

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

A. So, again, it is a very complicated question. Clinical trials have many specific requirements so that they would be understood and describe the rationale, the risks, the inclusion criteria, the analysis. And so writing the clinical trial involves being responsible for the teams that collaborate with all the different parts of putting together a clinical trial.

Q. And you mentioned that as a principal investigator, you were involved with submitting a clinical trial for approval. What's involved with submitting a clinical

trial for approval?

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

A. So I was specifically referring to getting it approved at one institution so that one can enroll patients, and at a minimum, that involves, at a minimum, submitting the study and some rationale for the study to a scientific review committee, as well as an institutional review board, or IRB, to obtain approval for that study.

In most institutions, like the ones I've practiced in, there are many other layers of requirement to understand how the funding and the resources, the feasibility, patient population, there is a lot of variables that go into those decisions.

Q. And have you been involved in dealing with those other variables in the clinical trials that you have participated in?

A. So, yes, so certainly in my role currently I'm the director of the GI disease management group at NYU, DMG. And what that role essentially means is that if any

investigator within GI cancers has a protocol, it has to go through our committee to determine whether all of those steps are going to be met adequately.

Q. Do you prescribe Keytruda to the colorectal cancer patients that you treat?

A. To some of them when appropriate.

Q. And how do you determine when it's appropriate to prescribe Keytruda to a colorectal cancer patient?

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

A. So, again, that is a very broad and long discussion. I can only reiterate that, you know, almost everything we do is based on teams and collective knowledge.

So generally, either we're relying on what's printed, so we go to clinical trial -- I'm sorry, to NCCN or compendia guidelines, which are expert opinion, or like at NYU, we have what are called tumor boards, where we discuss complicated patients, and the discussion will involve literature that's known, the experience of different

investigators, the health of the patient, and make a determination whether this is a medication that would be likely to benefit and it's indicated for that patient.

Q. Do you routinely test your colorectal cancer patients for MSI-high?

A. Yes, our institution tests every single colorectal cancer patient for MSI-high.

Q. Okay. And if a colorectal cancer patient -- if their MSI-high test comes back positive, what happens?

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

A. Can you clarify what you mean by "what happens"?

Q. Uh-huh.

Do you use the results of that MSI-high testing that you perform on colorectal cancer patients in making treatment decisions for the patient?

A. So one of the reasons that we test for MSI-high and have done this for many, many years is that MSI-high could be a marker for genetic syndrome that predisposes someone and

potentially their family to develop colon cancer and other cancers.

So one aspect of MSI-high testing is referral to a genetics counselor to understand whether that's a fundamental or germline mutation, and that is something that we certainly do.

That may have significant impacts on that person's screening for other cancers, as well as the treatment of their cancer, and potentially family who may have the same genes as they have.

Q. And when you're talking about germline mutations, you're talking about Lynch syndrome; correct?

A. Correct. The name for a germline mutation in an MMR protein is Lynch syndrome.

Q. Okay. If you have a colorectal cancer patient who is MSI-high, would that affect your decision whether or not to prescribe that patient Keytruda?

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

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.

The role of immunotherapy is

currently only relevant in the metastatic patients.

Q. And what is the definition of metastatic?

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

A. So generally metastatic is used to describe one of two things, either a cancer that, as I said, is not curable by removing it, so it can't be removed through surgery or some other means, and thus, it's, quote/unquote, incurable by surgery, or a cancer that has spread from its original site of origin.

Q. How does metastatic cancer that is incurable by surgery differ from cancer that's unreceptible?

A. So if you're using the terminology in that sentence, metastatic cancer that's incurable by surgery means that the metastatic cancer has spread from where it started and there is evidence that cancer cells have gone somewhere else from the site of origin.

Q. Can you have metastatic cancer that

has not spread from where it started?

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

A. So as I said earlier, it depends on what context one is using the terminology "metastatic." If you use it in the context of metastatic cancer that is not surgically removable, it would imply two separate things. It has spread and it's not surgically removable.

If one just calls the cancer incurable or metastatic, it may refer to a cancer that is in its local spot, but has spread to such an extent to the local tissue that is incurable and unremovable by surgery.

Q. So how does that metastatic cancer that has spread to such an extent in the local tissue that's incurable differ from locally advanced cancer?

A. So --

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

A. Yeah, so there are not really

standard definitions for many of these materials, so, for example, locally advanced cancer is really not an accepted terminology that can transfer from one physician to another physician, meaning one surgeon may look at something and say, This can never come out. It's locally advanced, and another surgeon can look at it and say, I have no problem doing surgery here.

So there isn't anything biological that we can use to define locally advanced, and generally, we leave it up to the person who is evaluating the patient.

Q. So in your opinion, there is no standard definition of locally advanced cancer?

A. I can't speak for all cancers, but for GI cancers, that is generally accurate. There is no standard definition.

Q. In your practice, do you prescribe Keytruda to colorectal cancer patients who are MSI-high?

A. Sometimes I do, yes.

Q. And in your practice, do you

prescribe Keytruda to colorectal cancer patients who are not MSI-high?

A. So I generally do not, outside of a clinical trial or some very rare exceptions.

Q. As part of your practice, do you regularly read the medical literature?

A. So the medical literature is a very broad term. Certainly spent a considerable amount of time reading medical literature. I hardly make a dent in what's out there by doing that.

Q. So what is your process for identifying the most relevant medical literature to review?

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

A. So I have a few processes. One is I get a daily listing from some cultivated service that tells me what they think is important in the literature, and I do my own independent reading, and I receive journals in my home that I look at, usually online actually nowadays, but I also work within a group and we have regular meetings, and it's

sort of an opportunity for people who have found something that they think is relevant, to share it with the group and discuss what it might mean. So we attend things called journal club and other educational meetings, as well as larger meetings with key opinion leaders and Congress meetings.

Q. You mentioned that you look at journals online. Which journals do you read online?

A. So I would say it's an evolving cast. I currently look at Nature, Journal of Clinical Oncology. Often the New England Journal of Medicine and a journal called Science. In addition, I receive other journals, and I, again, look at many things, depending on whether the headline that is relevant to me and catches my interest.

Q. And why did you pick those journals to review?

A. The primary reason is that if one serves as a reviewer for a journal, they usually get a complementary subscription to that journal, and then they just start sending

that to you.

Sometimes they stop after a year and sometimes they never stop. So these are all journals that at some point, I probably engaged with them, and they started sending things to me, and they're of interest.

Q. And would you say that those journals are highly respected journals?

A. In general, yes. I don't agree with everything I read, but yes.

Q. So you don't agree with everything you read even in highly respected journals?

A. Correct.

Q. Okay. Are you aware of any research in the field of oncology that was later retracted or corrected?

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

A. What do you mean by "the field of oncology"?

Q. So you review journals as part of your medical practice; correct?

A. (No response.)

Q. And I'm assuming that those are

journal articles that are relevant to your oncology practice; correct?

A. That is correct.

Q. Okay. So of those journal articles that you review that are relevant to your oncology practice, do you remember any that have been either corrected or retracted?

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

A. So it's very common to have corrections, which are usually editorial corrections, of the name or the spelling in a journal. It's exceedingly rare for a journal printed in a high impact publication to be retracted.

And I could think of very few examples of that, and say it's much more likely that a journal describing very preliminary scientific work, that is almost speculative, would be retracted, but in the publications that I mentioned, I think it's exceedingly rare for an article to be retracted, and I can't recall a specific example in GI cancer that comes to mind.

Q. Okay. And sometimes when journal articles are published, the journal will also publish letters or comments on those articles; correct?

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

A. So that is correct, but it's highly variable based on the journal as to what format those take and how much review or peer review those undergo.

Q. And sometimes those letters or comments can come from authors who disagree with the journal article; correct?

A. So again, it depends on the journal. Some journals will not publish such an article or letter and some will.

Q. Which journals will publish those type of letters or comments?

A. So I don't think journals release their official editorial stance, and I think a lot of it depends on the editorial decision making of the editors of that journal.

Q. Uh-huh.

A. The New England Journal of Medicine

does occasionally publish critical letters. They almost never critique the primary finding of the study and they almost always discuss the implication of that study and what the author said versus what the arguer or discusser thinks.

Q. So there can be a disagreement in sort of the medical community about what the implications of a given reference are; correct?

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

A. Again, that's incredibly broad statement. It depends on the article and what it's arguing and whether there is room for a different interpretation of those facts or a disagreement with the facts.

Q. But that happens sometimes; right?

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

A. I would say in clinical trials, in clinical trial research, it's exceedingly rare that someone would challenge the fundamental 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.

Q. Uh-huh.

A. Most reviewers, including myself, will always look at a document that's submitted for a clinical trial publication and make sure that it matches what was reported in the clinical trial record at the initiation of the study, and it always does.

Q. And you previously testified that some medical literature will contain speculative statements; correct?

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

A. So I can't speak for all medical literature. I think specifically the journals that I mentioned earlier, again, speaking that there are editors of these journals who make these decisions, but they almost always were not encouraged or would prohibit a speculative statement.

In a journal you'd have to support what you're saying with the facts of what you have in the article. There are many, many other journals that are published that may

have different standards.

Q. And as a reader of a given article or reference, would you approach a speculative statement more critically than you would sort of a factual statement about the results of a trial or something like that?

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

A. So I think those statements would be stated very differently, right. If someone said a definitive conclusion, that would be taken in a different light than if they said a speculative statement.

Q. Uh-huh.

A. I think both would be taken seriously if you take seriously the author of the study.

Q. Uh-huh.

A. But they have different implications.

Q. And what are those different implications?

A. One is speculation and one is definitive.

Q. Uh-huh.

And as a reader of an article, would you be more critical or maybe have, you know, read more closely that speculative statement than you would that factual statement?

ATTORNEY RATLIFF: Which article, which speculative statement are you talking about?

Q. So --

A. Yes, can you clarify -- sorry, I'll repeat that.

Q. Okay.

A. But this is getting very abstract and vague. I mean, I think in general, a person would read an article and have the same level of belief in that article based on the authors and the journal regardless of what the statement is, but again, if you have a specific example, I perhaps can comment on it.

ATTORNEY RATLIFF: Counsel, we've been going about an hour. While you're searching for a question, let's take a break.

ATTORNEY BROWN-MARSHALL: We'll take a break.

THE WITNESS: A break.

CERTIFIED STENOGRAPHER: Off the stenographic record at 10:16 a.m.

- - -

(Whereupon, a short recess was taken.)

- - -

CERTIFIED STENOGRAPHER: Back on the stenographic record at 10:29 a.m.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, as part of your medical practice, do you monitor postings on ClinicalTrials.gov

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

Q. Do you read postings on ClinicalTrials.gov

A. So, yes, I frequently do.

Q. Okay. And are those postings, are those related to clinical trials that you are participating in?

A. So I review a very large number of postings to be honest, I engage in many clinical trials, but, you know, one of the primary uses of ClinicalTrials.gov to me and

others like me, I think is as we referenced here in Benson I believe, one of the recommended treatments for any metastatic colorectal cancer patient beyond second line therapy is clinical trials, and so very often we'll have a patient in which we know that we should consider clinical trials, and since I don't have offhand knowledge of every single clinical trial, I'll often go to ClinicalTrials.gov, put in their disease and their stage and things like that and look for trials. Patients will often do the same thing and come to me and give me a trial number and ask me what I think about a trial.

Q. So other than identifying potential trials for patients, are there any other reasons why you'd check postings on ClinicalTrials.gov

A. Yeah, so I think, for example, someone will call me up and say, We have this new compound we're interested in testing in new clinical trials.

The first thing you would do is look at ClinicalTrials.gov to see if it's

already being tested and what context and learn information from that as well. It's very often one of the primary public sources of information about ongoing clinical trials for a particular drug.

Q. And do you limit your review of postings to ClinicalTrials.gov to specific diseases?

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

A. So I'm not sure what you mean by that. I treat specific diseases and do research on specific diseases, and that's what I'm primarily interested in. However, there are many, many medications that are being tested in a different setting that would have relevance to the disease that I treat or the setting in which I want to use it in.

Q. And when you read a submission on ClinicalTrials.gov related to a clinical trial, do you read that submission with the assumption that that trial will be successful?

A. So that's an incredibly vague question and it really depends on the trial,

what I know about it, you know, the information, the setting, the sponsor, you know, I incorporate all of the information there to make that decision.

Q. So you read those submissions with an eye towards sort of evaluating how successful you think the trial might be based on those factors that you just described?

A. So I don't think that was an exhaustive list of factors, meaning, I think it's hard to give a single answer for every single posting on ClinicalTrials.gov about the desire to participate in that trial and what we mean by the likelihood of success or ability for a certain patient to go on that trial.

Q. But you sort of review a clinical trial that you might be considering for a patient with a critical eye in that you need to evaluate what you think is the sort of the value of that trial?

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

A. So I'm not sure what you mean by "a critical eye." I think we certainly want to be good stewards and give the right treatment to the right person.

Q. And part of that being a good steward is evaluating what you think the potential success of a clinical trial would be before you enroll a patient in that trial?

A. So I would certainly want to make sure that it's worthwhile for a patient to go on a trial before recommending the trial to that patient.

Q. And you noted in your declaration that: My focus on multidisciplinary collaboration has led to rapid access referrals of patients in our clinics and increased clinical trial participation by over 100 percent; is that correct?

A. That is correct.

Q. Okay. Why is it important to increase clinical trial participation by over 100 percent?

A. I'm trying to find it. So there are many reasons likely for trials are

valuable. One of the reasons, as I just mentioned, is that for many patients, clinical trials are part of what we consider the standard of care, and thus ideally, every patient with colon cancer who has treated with two prior regimens, excuse me, would have a clinical trial that they can participate in, if appropriate.

So the reality is that clinical trials open and close and are for different cohorts and they're very specific, so by increasing both awareness of clinical trials, increasing the range of clinical trials, we're able to give more options to patients.

Q. And are clinical trials the method by which new methods of treatment are identified?

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

A. So I'm sorry, what do you mean by "methods of treatment"?

Q. So one of the purposes of a clinical trial could be to evaluate a new use for a known drug; correct?

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

A. That is correct.

Q. And -- so increasing participation in clinical trials would help support the evaluation of new uses for known drugs; correct?

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

A. So not necessarily. There are many clinical trials that don't lead to new uses of drugs, but potentially.

Q. What are the other potential benefits of expanded participation in clinical trials?

A. So, again, the primary benefit for a patient is to have access to more options for therapy to treat their cancer, help them have a better outcome.

Q. So going beyond an individual patient, are there benefits to sort of patients writ large to increasing participation in clinical trials?

ATTORNEY RATLIFF: I object to the form

of the question.

A. So I'm not sure what you mean by "patients writ large." Not the person who's on the trial? Somebody else?

Q. Are there benefits to, let's say, colorectal cancer patients as a collective to increasing participation in clinical trials?

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

A. So I wouldn't say clinical trials per se. It really depends on the quality of the clinical trials.

Q. Uh-huh.

A. You know, if they're clinical trials that are of quality that they're likely to give new understanding of how to treat a patient, then certainly that could have relevance for, as you put it, the community at large, the community at writ large I guess, but that's why we evaluate clinical trials and we decide, you know, whether this is an appropriate -- or not appropriate, whether this is a clinical trial that is likely to benefit our patients and it is something that

fits within our sphere of treatment.

Q. And, Dr. Oberstein, you have a master's in biostatistics from Columbia; correct?

A. That's correct.

Q. Why did you obtain that degree?

A. Why did I obtain?

Q. Uh-huh.

A. So that degree was done in a federally funded grant program, meaning I submitted a grant, an application was awarded, and they paid for my degree, to support me as what was called a patient oriented research fellowship. And the goal I think of that underlying federal grant is to increase the number of physicians and researchers who are applying the techniques of research for patient-specific cares.

My aspect of that was clinical trial design and clinical trial conduct, and so one of the really important parts of clinical trials is the statistics part of it, to make sure that we are asking questions that we can answer in the context of a clinical

trial, and that at the end of a successful trial, will have an answer to that question.

Q. And that statistical training, that's not something that you learn as part of your medical training; correct?

A. So it's absolutely essential to have some basic statistical knowledge as part of medical training and more specifically in oncology, which is a very trial heavy field. We do a lot of clinical trials. As you see, that's one of the standard of cares for a patient. This was well above that. So I did more advanced techniques in statistics in dedicated courses in biostatistics.

Q. And how have you used that sort of advanced statistical knowledge in your medical practice?

A. So I use it frequently when I both evaluate clinical trials, when I talk to our biostatisticians about designing prospective studies, but primarily in educating our fellows and our junior faculty about how they could use statistics to look at the literature, look at the data that's printed

and understand what exactly it's telling us and how to utilize it in their practice.

Q. And as part of your practice, you are involved in designing and conducting clinical trials; correct?

A. That is correct.

Q. And those clinical trials that you have designed and conducted involve using novel agents, including immunotherapies, for the treatment of colorectal, pancreatic, and other GI cancer patients; correct?

A. That is correct.

Q. How many clinical trials have you designed?

A. So it's a little bit difficult to give an exact answer to that question, because as I think I mentioned a few times, clinical trials really require a very large team of participants for many, many different aspects of the trial, and so there are some that I was the principal investigator and the primary, quote/unquote, designer.

Q. Uh-huh.

A. But there are many, many, many

studies in which I have a role as one of the consultants or one of the key opinion leaders in helping provide direction and design for that trial. So including the more broad definition, I would say probably 30 or 40 clinical trials, but it's hard to give an exact number.

Of the trials that I've primarily designed and conducted on my own, it's probably in the 5 to 10 number.

Q. And were you the principal investigator on those 5 to 10 trials?

A. Generally.

Q. And what does it mean to be a principal investigator on a clinical trial?

A. So, again, a principal investigator can mean many different things and these terminologies are all quite varied depending on the context, so perhaps you can give me some more perhaps to what you mean.

Q. Well, you used the term "principal investigator." I'm just trying to figure out what you mean by it when you use it?

ATTORNEY RATLIFF: If that's a

question, I object to the form of the question.

A. So let me do perhaps the most common use is that each site, each institution or site, has to have one person who is responsible for overseeing all aspects of the trial and is accountable, and that person is called the principal investigator.

Q. Uh-huh.

A. In general, that person may or may not have been the one who designed the trial, but at that site for which they serve as principal investigator, they ultimately have responsibility of all of the people involved in the regulatory, the clinical conduct, the reporting, and other aspects of the clinical trial, and need to be familiar with that.

Q. Do clinical trials usually have a sort of primary principal investigator?

A. So I would say there is really no usual with clinical trials. Some do and some don't. There is really as many flavors as you can imagine.

Q. When you make a submission to

ClinicalTrials.gov, do you need to identify the principal investigator on your submission?

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

A. So in general, in ClinicalTrials.gov, you identify -- I think the term is a study official, which is usually someone in which the, I guess, the HHS or NIH can contact that person for information. That's not always the principal investigator, though sometimes it is.

So just, for example, by mistake someone recently posted a clinical trial that included my cell phone number as the principal contact. My phone was ringing off the hook until we corrected that. So that could happen. I was not the principal investigator and that was inappropriate, but very often they will include a contact, but not always.

So it always has to include a contact for the FDA to reach out to, but not always the principal investigator.

Q. So of those 5 to 10 clinical trials that you were responsible for designing, how

many of those were -- involved immunotherapies?

A. The majority of them.

Q. And which immunotherapies did those involve?

A. So as I recall, this is not a comprehensive list, some included pembrolizumab in combination with chemotherapy. I recently did a clinical trial with a drug called camrelizumab. One with a drug called spartalizumab. And I'm the principal investigator of another trial with an immunotherapy whose name I can't recall or pronounce right now.

Q. So the clinical trial with camrelizumab, what sort of immunotherapy is that?

A. So I misspoke. Camrelizumab is an immunotherapy. I was not the principal investigator of that trial. The one I meant was canakinumab.

Q. And what type of immunotherapy is canakinumab?

A. That is an antibody, again,

something called IL-1 beta.

Q. So not a checkpoint inhibitor?

A. Not a checkpoint inhibitor.

Q. Okay.

A. I -- I -- I don't know if you want background. IL-I beta involves something called MDSCs, or myeloid derived suppressor cells.

Q. And you also mentioned a clinical trial involving spartalizumab?

A. Correct.

Q. What type of immunotherapy is that?

A. Spartalizumab is a PD-1 enteron.

Q. And do you know who makes that antibody?

A. Novartis provided the drug to me for the study, but I think they've given up on or passed it on to someone else.

Q. So clinical trials are classified by phases; correct?

A. Correct.

Q. Okay. And there is a Phase I, a Phase II, and a Phase III?

A. And a lot of gray area in between.

Q. Okay. What is a Phase I trial?

A. So, again, these descriptions are not 100 percent clear-cut, and there is very little that limits a person from describing their trial within one context, even if it crosses a gray area, but traditional Phase I clinical trials were meant to discover whether an agent or a drug is safe and to find a maximum tolerated dose that that drug can be given to to people in a certain circumstance.

Q. And what's a Phase II trial?

A. So, again, traditionally a Phase II trial was done after a Phase I, when a dose was identified, to try to determine whether there is any evidence of that dose would have a beneficial effect on people or whoever was being tested in that Phase II trial.

Q. And what is a Phase III trial?

A. So, again, in the most simple terms, a Phase III trial is done if a Phase II trial shows that there is some effect of the medication, to try to determine whether the medication is better than a standard alternative medication, utilizing a much

higher level of statistical significance and standards than in a Phase II.

Q. And are Phase III trials generally larger than Phase II trials?

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

A. So, again, it's very hard to give generality for clinical trials, because it would depend on the target and the specific indication and statistical method being used. In many circumstances, Phase III trials are larger, but it's not necessarily the case.

Q. And I've seen some labels for sort of intermediate levels. Are you familiar with a Phase IIB trial?

A. So, again, these terminology are not defined and people sort of make them up for their own trial. There is an intent. Very often, and not always, a Phase IIB trial would be a Phase II trial where you're trying to determine efficacy, but you do it in a randomized fashion to include some kind of a control group, even though statistically it's not as powerful or as large or as definitive

as a Phase III trial, but you can get some preliminary data. That is one use of Phase IIB trials. It's not the only use of them.

Q. What are some other uses of Phase IIB trials?

A. So, again, anyone can call their trial a Phase IIB trial, there is no limitation, but someone might do that if it's sort of a second step they did a Phase II trial, gathered information, but want to gather even more information.

Q. And clinical trials can be prospective or retrospective; correct?

A. So in general, yes.

Q. Okay. And what is a prospective clinical trial?

A. So, again, in the simplest terms, a prospective clinical trial is where the patients are identified and being placed on a trial before they are treated, before the question that you're addressing the trial is asked.

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

develop colon cancer.

20 years later, we take all of that data and we retrospectively go back and look for factors that may contribute to that thing happening. So that's a prospectively collected, retrospectively analyzed trial, that would be considered a very weak trial in our fields.

Q. And a clinical trial can be randomized or nonrandomized; correct?

A. Again, those are both possibilities in a clinical trial, yes.

Q. Okay. What is a randomized clinical trial?

A. So there are many ways to randomize, but often a clinical trial that's randomized is a trial in which a patient is enrolled in the trial without anyone or without them knowing what they're going to receive in the trial, and at some point after enrollment, the randomization occurs and they're placed into an arm in that trial.

Q. And does that involve randomly assigning the treatment method that they're

going to receive as part of the clinical trial?

A. I don't understand the question.

Q. So if patients are randomized to different arms, they can be randomized to different methods of treatment, correct, if those arms have different methods of treatment?

A. Or no treatment.

Q. Or no treatment.

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

Q. Are there ways that patients can be randomized that don't implicate the method of treatment in a clinical trial?

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

A. I don't think I understand the question.

Q. So the example we were talking about is patients being randomized to different arms of a clinical trial where those different arms received different methods of treatment or no treatment; correct?

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?

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

A. So I think a person of ordinary skill in the art would have to look at the information that's in front of them, and I don't think I can answer without seeing the specific information that that person would then utilize to determine whether it's randomized or not randomized.

Q. Would that randomization or nonrandomization, would that be limited to assignment to arms in the clinical trial?

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

A. I think you already asked that, but again, it really depends on what's written in the document and what the person of ordinary skill would see in front of them to make that determination.

Q. What clues would be written in the document that would tell them how randomized or nonrandomized should be interpreted?

A. I think we're talking about a theoretical document. If you show me a

document, I can point to you to what I think would be valid in that document.

Q. Well, you mentioned that there could be tons of variables that are randomized within a clinical trial; right?

A. Correct.

Q. How would a person reading a ClinicalTrials.gov submission related to a trial figure out which variables are randomized and which ones are not?

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

A. So a person of ordinary skill would look at the document in front of them, and again, if you give me a specific example, I can look at it and give you my judgment as a person of ordinary skill how they would evaluate that document, but theoretically, I can't answer the question without seeing what you're referring to.

Q. Do ClinicalTrials.gov submissions generally contain information on all the possible variables in a given clinical trial?

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.

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

pembrolizumab in patients with microsatellite unstable tumors, I think this trial specifically was to test whether the response rate and question of the survival would be improved in patients with MSI-high colorectal cancer treated with pembrolizumab.

Q. That was not my question.

At a general level, can in vitro data serve as a possible rationale for a clinical trial?

ATTORNEY RATLIFF: I think that was the response to your question, and also note that the court reporter moved over a second monitor for questioning counselor to see. We are having trouble with the realtime. It stopped over here.

ATTORNEY BROWN-MARSHALL: My realtime stopped too.

CERTIFIED STENOGRAPHER: Do you want to go off the record?

ATTORNEY RATLIFF: Yes, please.

ATTORNEY BROWN-MARSHALL: Yes, sir, please.

CERTIFIED STENOGRAPHER: Off the

stenographic record at 11:05 a.m.

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(Whereupon, a short recess was taken.)

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CERTIFIED STENOGRAPHER: Back on the stenographic record at 11:15 a.m.

BY ATTORNEY BROWN-MARSHALL:

Q. So, Doctor, before we get back to my question that is pending when your counsel unilaterally decided to take a break, I need to ask you: Have you had any conversations with counsel during any of the breaks we've taken today regarding the substance of your testimony?

A. No, I've not.

Q. So getting back to my question, can in vitro data serve as a possible rationale for starting a clinical trial?

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

A. So, again, it's an incredibly broad question, but I -- maybe you can clarify what you mean by in vitro data as opposed to what?

Q. In vitro data as opposed to in vivo data?

ATTORNEY RATLIFF: Same objections.

A. So I can't speak for every clinical trial, and I think it's possible that someone could submit a rationale to start a trial with in vitro data alone.

Q. Okay. And can in vivo animal data serve as the basis for the rationale of a clinical trial?

A. Again, it depends on what clinical trial and what stage clinical trial, but there certainly are early stage trials that might be done based on in vivo animal data.

Q. And how does the stage of a clinical trial affect the types of data that might serve as the rationale?

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

A. So as I described earlier, a Phase II clinical trial generally is done after a Phase I clinical trial and thus wouldn't be done without a Phase I clinical

trial ahead of it to show a safe and maximum tolerable or effective recommended Phase II dose of a trial.

Q. And the Phase I, Phase II, Phase III trials, then those are generally sequential?

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

A. So sometimes.

Q. Sometimes?

A. (Indicating.)

Q. When are they not sequential?

A. Again, there are no hard rules about a trial, and there are times where a study might do a Phase I and then a Phase III or skip certain steps along the way. It all depends on the context and the findings and the individual details of the trial.

Q. What would be the motivation for skipping from a Phase I trial directly to a Phase III trial?

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

A. So it depends on the trial. I would expect to evaluate a clinical trial based on the prior art known before that trial time point when I'm making that assessment and what's available to a person of ordinary skill to determine this likelihood or possibility of success in that clinical trial. It would vary greatly depending on the specifics of the trial and other information in the art and literature.

Q. What is the general success rate for clinical trials?

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

A. So I don't think one can answer that question, because clinical trials are not one category of things. It really depends on the type of clinical trial, the information that was known prior to the trial, whether it was the first use of a drug or a subsequent use of the drug or a phase of the trial.

So I think a specific trial we can potentially give some information, but it 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

trial I've participated in.

ATTORNEY BROWN-MARSHALL: I'd like to mark this as Exhibit 2405.

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(Whereupon, document entitled Gastrointestinal Cancer - Gastroesophageal, Pancreatic, and Hepatobilia 4042, is received and marked as Exhibit 2405 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2405.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, the court reporter has just handed you Exhibit 2405.

Are you familiar with this document?

ATTORNEY RATLIFF: And I will object to Exhibit 2405 for the purposes of authentication, foundation, and hearsay.

A. Yes, I'm familiar with this abstract.

Q. Okay. And what is this abstract?

A. So this is an abstract describing a Phase II clinical trial of Lenvatinib plus

pembrolizumab for patients with immunotherapy naive advanced gastric cancer following first-line therapy.

Q. And you are one of the authors on this abstract; correct?

A. That is correct.

Q. Okay. And did you participate in the clinical trial described in this abstract?

A. Yes, I did.

Q. Okay. What was your role in that clinical trial?

A. I enroll patients in the clinical trial, and ultimately when the first investigator named here left our institution, I took over her role as the principal investigator for the conclusion of the trial.

Q. Okay. And did this specific clinical trial have a rationale?

A. Yes.

Q. Okay. And what was the rationale for this clinical trial?

A. So the rationale of this clinical trial was that treating with -- cancer with a drug that focuses on blood vessels or

angiogenesis would make tumors more susceptible to immunotherapy and thus the combination of an antiangiogenic treatment plus immunotherapy treatment would be efficacious.

Q. And that rationale was based on preclinical studies; correct?

A. It was based on preclinical studies, as well as clinical studies, as this combination is used in other cancers with efficacy.

Q. And this clinical trial, you were testing a hypothesis that the combination of VEGF inhibition and ICI may be more beneficial than either agent alone; correct?

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

A. So that was the hypothesis in this clinical trial, correct.

Q. Okay. And when you say ICI, you're referring to immune checkpoint inhibitors; correct?

A. Yes.

Q. And the immune checkpoint inhibitor

that you tested in this trial was pembrolizumab; correct?

A. That is correct.

Q. What was the result of this clinical trial?

A. So this clinical trial it would describe here was designed to determine whether we can achieve a response rate of 20 percent or so.

And ultimately, we had to stop the trial before we finished it because the standard of care of treatment for gastro cancer changed during the course of the trial.

So we did not get complete results from the trial, but the preliminary result of those 24 patients who were enrolled were that 20 percent of them responded to treatment, but that was less than what we were anticipated seeing because we had to stop the study early.

Q. And for this study, it did not meet the primary endpoint in ICI-naive cancers; correct?

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

A. That is correct.

Q. Why were you testing in ICI-naive patients?

A. Because at the time we started this study, there was no FDA approval or wide use of immune checkpoint inhibition in first-line treatment of gastric cancer.

Q. So why would that motivate you to test in ICI-naive patients?

A. Because we suspected that should we move forward with this combination, that's who would get it. We wanted to have a relevant patient population.

Q. So for this specific study, when you started this study, did you anticipate that it would be successful?

A. So as I clarified, I was not involved in starting this study. I came into the study in the middle of the course of the study.

Q. Uh-huh.

A. But -- so I can't answer for the person who started the study.

Q. So at the point that you joined the

study, did you anticipate the study would be successful?

A. I did.

Q. You can put that aside.

ATTORNEY BROWN-MARSHALL: So I'm handing the court reporter an exhibit that I would like to mark as 2406.

- - -

(Whereupon, document headed HHS Public Access, is received and marked as Exhibit 2406 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2406.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, are you familiar with this exhibit?

ATTORNEY RATLIFF: I will object to Exhibit 2406 for the purposes of authentication, foundation, and hearsay.

A. Yes, I'm familiar with this publication.

Q. Okay. And are you an author on this publication?

A. Yes, I am.

Q. What is this publication?

A. So this publication describes the results from a Phase IIB randomized multicenter study of something called GVAX pancreas vaccine and CRS207, compared with chemotherapy in adults previously treated with metastatic pancreatic adenocarcinoma.

Q. And the first author of this publication is Dung Le; correct?

A. That is correct.

Q. And did you work with Dr. Le during the course of this clinical trial?

A. Yes.

Q. Have you worked with Dr. Le before?

A. So just to clarify, when you say "worked with," we participated on group calls together to discuss the progress of the trial.

Q. Uh-huh.

A. I participated on calls with Dr. Le before this, yes.

Q. Okay. And what was your role in this trial?

A. So I as I recall was a principal investigator of this trial at my site, which

was at Columbia at the time.

Q. Okay. And were you involved in the design of this clinical trial?

A. I don't recall my exact role in the design of the trial. I don't recall. So I may have been, but I can't recall.

Q. Okay. Was Dr. Le involved in the design of this clinical trial?

A. I can't speak for Dr. Le.

Q. Okay. And this trial tested GVAX pancreas and CRS207, compared with chemotherapy in adults with previously treated metastatic pancreatic adenocarcinoma; correct?

A. That is correct.

Q. What is GVAX pancreas?

A. So GVAX pancreas is a type of a vaccine that is injected into patients and meant to stimulate an immunoresponse against their tumor.

It specifically stimulates something called granulocyte macrophage colony stimulating factor secreting --

- - -

(Clarification requested by the

stenographer.)

A. CSF for colony stimulating factor secreting tumor cells from pancreatic cancer cell lines to induce an immunoresponse in the patient.

Q. So you would consider GVAX pancreas as a type of immunotherapy?

A. I would say it's a type of vaccine, so it depends on how you qualify immunotherapy. It's not a checkpoint therapy, but it's certainly something that is meant to stimulate the immune system.

Q. Well, would you categorize GVAX pancreas vaccine as an immunotherapy?

A. Again, I think generally we think of it as a vaccine therapy, which is possibly a subset, but not usually classified as immunotherapy.

Q. So you don't consider vaccines to be a subset of immunotherapies?

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

A. I don't think there is a standard definition. I think very often when people

talk about immunotherapy for cancer, they're referring to immune checkpoint therapy or immune stimulatory therapy, not vaccine therapy, which gets its own sort of classification, but vaccines do work by affecting the immune system.

Q. What was the rationale for the clinical trial in Exhibit 2406?

A. I can't definitively speak to that because I was not the primary person who designed the trial.

Q. What was your understanding of the rationale?

A. So my understanding, again, this is my recollection years later, is that this was a vaccine that Hopkins was developing for use in pancreatic cancer, and they had had very little success with it overall over many years, except in two people who were on a different clinical trial, who received this other medication called CRS207, who received that medication, coincidentally went on a clinical trial with the vaccine and then seemed to do quite well. So they hypothesized

that there was some connection between those two things.

Q. And that was based on the results of those two patients?

A. That's my recollection.

Q. Okay.

A. I was not involved with treating those patients and those studies were not done with my supervision.

Q. And this article talks about CRS207, what is that?

A. So CRS207 is basically a live bacteria. So you inject bacteria into patients. It's attenuated so that it doesn't cause severe illness, but it causes them to get pretty sick because it is live bacteria, and the hope and expectation is that that will cause their immune system to target the bacteria and also target the cancer.

Q. So is CRS207 then given in conjunction with the GVAX pancreas vaccine in this clinical trial?

A. So there were three arms in this clinical trial. Arm 1 got a combination of

the GVAX pancreas vaccine in CRS207; Arm 2 got CRS207 alone without the vaccine; and Arm 3 received chemotherapy.

Q. And what were the results of this clinical trial?

A. So the results of the clinical trial were that the overall survival in the true group that got GVAX plus CRX207 was not different than those who got chemotherapy. So it was not improved as had been hypothesized.

Q. So the study failed to meet its primary efficacy endpoint; correct?

A. That is correct.

Q. And when you joined the study, did you anticipate that the study would be successful?

A. Yes, I did.

Q. And that was based on the data related to the treatment of the two patients --

A. There was additional data as well. So prior to this Phase IIB study, they conducted a 2A study where they gave similar treatments to look at different doses that

might be effective.

Q. Okay.

A. I was not part of the study, but I knew the data from it.

Q. So the rationale was based on those two patients that were treated at Johns Hopkins and had a successful response and results of that Phase IIA study; correct?

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

A. So I believe so.

Q. Okay. And in spite of that promising data, the study still failed to meet its primary endpoint?

A. So I would say despite that preliminary data.

Q. It still failed to meet its primary endpoint?

A. This study did fail to meet its primary endpoint, correct.

Q. You can put that aside.

So as part of your work designing and conducting clinical trials, do you have

any experience with the ClinicalTrials.gov website?

A. What do you mean by "experience"?

Q. Have you ever made submissions to ClinicalTrials.gov in conjunction with a clinical trial that you either designed or conducted?

A. Yeah, yes, but I didn't personally make the submissions. We have a regulatory coordinator who does the submissions. I have to approve them if they're done for my trial.

Q. Okay. Are you involved in drafting those submissions to ClinicalTrials.gov

A. I certainly approve them before they're posted.

Q. But you have a team that assists you in drafting and actually posting them?

A. We definitely have a team that's part of our regulatory control to make sure we do everything we have to do before starting the study.

Q. Are submissions to ClinicalTrials.gov required for human clinical 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.

There are requirements in certain necessary fields, but there is certainly leeway for the investigator to add information or include information based on what they want to do.

Q. So how does the public use the information that's posted on ClinicalTrials.gov

ATTORNEY RATLIFF: Every single person in the world you're asking about?

A. Sorry, so can you clarify what you mean by that?

Q. Well, you agreed that submissions to ClinicalTrials.gov provide important information to the public; correct?

A. Yes, I agree with that.

Q. Okay. So how is that information used by the public?

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

A. So that's overly broad I would say because the public can encompass many, many people who are using it for many different purposes.

Q. Uh-huh.

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 submissions to ClinicalTrials.gov for the

purposes of the clinical trials that you work on?

A. You mean in addition to the federal requirements or separate from that?

Q. Do they have any requirements at all in conjunction with submissions to ClinicalTrials.gov

A. So I believe that we have a requirement that a trial be submitted on ClinicalTrials.gov before it can be opened and enrolling patients.

Q. So if a clinical trial involves a new drug or a new use for a known drug, you'll need to submit an IND; correct?

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

A. So I don't recall the exact requirements for when to submit an IND. I do recall the FDA has a very extensive website of the checklist that one fills out to determine whether their new study needs an IND. It's not as simple as I think you just put it.

Q. Okay. Let's back up.

What is an IND?

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

to get approval prior to the trial being able to proceed.

I'm sorry, let me correct that. Not so much the trial. Prior to the investigation being able to proceed.

Q. Is the IND holder generally a physician who's participating in the clinical trial?

A. It varies greatly depending on the nature of the trial. Not necessarily.

Q. Who else might be the IND holder for a clinical trial?

A. So other parties of the trial, such as the sponsor of the trial or pharmaceutical company or a clinical research organization that's organizing the trial can all be IND holders as far as I understand.

Q. And IND submissions made to FDA are confidential submissions; correct?

A. I'm not sure.

Q. Okay. Are you aware of any ways in which FDA makes IND submissions publicly available?

A. I'm not aware of any such ways.

Q. Are you the IND holder for any clinical studies?

A. Yes.

Q. Okay. Which ones?

A. Do you have my CV? Maybe that would help. Well, just for one example, that study you presented earlier, this study (indicating).

Q. Uh-huh.

A. I'm IND holder for this study.

Q. And you are holding up Exhibit 2405; correct?

A. 2405, correct.

Q. So you weren't the IND holder --

A. I didn't submit the IND because as I said, I took over the study. Someone left the institution. I stepped into that role. So by stepping into that role, I became the IND holder, and it's my responsibility to submit reports to the FDA about progress and data about the study.

Q. Okay. Have you ever prepared an IND for submission to the FDA?

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

has a long list. It's essentially a checklist that we go through to determine if your study is IND exempt or requires an IND.

Q. So in the INDs that you have reviewed, have you ever seen statements informing FDA that the IND holder did not think the study was going to work?

A. So I have submitted IND statements to the FDA and I have never submitted that. I can't speak for other people's IND submissions.

Q. Clinical trials may involve the evaluation of a biomarker; correct?

A. In general, that is correct. Again, very vague, but correct.

Q. Okay. And what is a biomarker?

A. So a biomarker, again, is quite a vague term, but it's something that is biologically or related to a tumor or a person that gives some information about how they will do or how they will respond to a therapy.

Q. And there are different types of biomarkers; correct?

ATTORNEY RATLIFF: I object to the form

of the question.

A. What do you mean by the question?

Q. So biomarkers can serve different purposes; correct?

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

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

Q. So are you familiar with the term "predictive biomarker"?

A. I'm familiar with the term, yes.

Q. Okay. What is a predictive biomarker?

A. So a predictive biomarker, again, like all these terminology, can mean different things in different settings, and so it would be helpful to see the exact context you're using it in.

In general, or sometimes people use it to be a prediction about whether a treatment or an intervention will help a person.

Q. And have you been involved in any clinical trials that evaluate a predictive

biomarker?

A. So I've been involved in many, many trials. I can't recall specifically.

Q. But sitting here today, you can't remember any clinical trial that you've been involved in that involved the evaluation of a predictive biomarker?

A. I think sitting here today, I don't have recollection right now.

Q. How many predictive biomarkers have been identified in conjunction with oncology therapies?

A. Again, that's a very broad question, and I think pretty much beyond the scope of what I was asked to evaluate here. I think there are many, but I can't give you a specific number. Oncology is a very broad field encompassing many tumors, many trials, many possible biomarkers, and I think there are many of them, but I can't recall every single one.

Q. And some predictive biomarkers will work in one type of cancer, but not in another 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.

Q. Okay. And when you do that, what

sort of testing do you perform on those colorectal cancer patients?

A. I'm sorry, can you clarify what you mean by that?

Q. So one way to test patients for biomarkers is to have their tumor more sequenced; correct?

A. That's correct.

Q. Okay. And when their tumor is sequenced, they're looking for the presence of certain biomarkers; correct?

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

A. There are many reasons to sequence a tumor. One of them may be to identify biomarkers, but there are many other reasons you may do it.

Q. What sort of biomarker-related testing do you order for your colorectal cancer patients?

A. So, again, some of it depends on the particular stage of the patient and their treatment options and whether this information is going to change what we do for the patient.

Some of the biomarkers that we look at are based on immunohistochemistry.

Some are based on PCR testing or next generation sequencing testing are the primary ways. We also utilize blood testing for many of those biomarkers, not tumor testing.

Q. And roughly, how many biomarkers do you have tested for your colorectal cancer patients?

A. Again, it's really hard to answer a general question. It depends on the person and the stage and the sample that's available for us. It can range from a very small number, to a very large number based on those factors.

Q. Okay. Ballpark, what is the very large number that you might be looking at?

A. So when we do next generation sequencing, our panel generally looks at 500 genes. Those are really the spectrum of all the genes that anyone who's ever had interest in.

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.

Q. And if a -- so if a researcher

posts the results of a clinical trial to ClinicalTrials.gov, those will appear in the study record; correct?

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

A. What do you mean by "the study record"?

Q. So on ClinicalTrials.gov, there are multiple tabs, one of which is the study record tab; correct?

A. I don't recall exactly what it looks like online.

Q. Does ClinicalTrials.gov post submissions related to the study record of a clinical trial?

A. What do you mean by "post submissions"?

Q. ClinicalTrials.gov is a website?

A. Correct.

Q. Researchers make submissions to ClinicalTrials.gov that are then posted on that website; correct?

A. That's correct.

Q. Okay. And one of the references

that you rely on in formulating your opinions is something that you refer to as the MSI-high study record; correct?

A. That is correct.

Q. So that is a June 10, 2013 submission of a version of a study record to ClinicalTrials.gov; correct?

ATTORNEY RATLIFF: Are you representing that to him?

ATTORNEY BROWN-MARSHALL: I'm asking him.

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

A. So the MSI-high study record that I referred to throughout my declaration is the one that I have that's posted on June 10, 2013, is ClinicalTrials.gov.

BY ATTORNEY BROWN-MARSHALL:

Q. Okay. And you can see from Exhibit 1005 that there are multiple submissions underneath that study record; correct?

A. That is correct.

Q. Okay. So I'm asking when a

researcher posts the results of a clinical trial to ClinicalTrials.gov, are those included as a submission in the study record for that clinical trial?

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

A. So I suspect that they are.

Q. Uh-huh.

A. When one goes online to ClinicalTrials.gov, there are tabs, which is what I thought you were referring to, and there is a separate tab now for study results.

Q. Okay.

A. I don't think it existed in 2015.

Q. Okay.

A. But I would have to confirm that.

Q. Okay. But now you think that you can go to ClinicalTrials.gov and click on a results tab and it will show you the results of the clinical trial?

A. If the investigators have posted the results.

Q. Okay. At what point would a treating oncologist rely on the results of a

clinical trial in making a treatment decision for one of their patients?

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

A. So that strongly depends on the nature of the clinical trial, the results of the trial, and what was known in the prior art to that treating oncologist at the time that they're making that decision.

Q. Would they wait until results of the clinical trial are available to make a decision to treat one of their patients based on that method?

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

A. As I stated, it depends on what was available to that oncologist in the prior art and what other information they have to make a determination.

Q. So that would be based on the publicly available information that that treating oncologist could access?

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

A. Is that something different than the prior art?

Q. Well, you used the term "prior art," and is it your understanding that prior art is publicly available?

A. Yes, it is.

Q. Okay. So if you're using the term "prior art," does that necessarily mean that the information that the treating oncologist is relying on is publicly available?

ATTORNEY RATLIFF: And by "treating oncologist," are you referring to every oncologist in the world?

ATTORNEY BROWN-MARSHALL: I'm referring to a treating oncologist.

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

A. So depending on the context and this person of ordinary skill who might be your treating oncologist, they would evaluate the information that's available to them in the prior art to make a decision as to whether or not to utilize the treatment.

BY ATTORNEY BROWN-MARSHALL:

Q. When a researcher is conducting a clinical trial, does statistical significance play a role in assessing the results of that trial?

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

A. So, again, it's a very broad question and will depend on the specific trial --

Q. Uh-huh.

A. -- what the results are; what statistics were planned for the trial; and what else is known in the prior art, probably among other things.

Q. Uh-huh.

A. But I think it's really hard to describe a general principle that will be true about all clinical trials, and we need to talk about a specific trial to answer that.

Q. How do you determine if a clinical trial has met its primary endpoint?

ATTORNEY RATLIFF: I object to the form 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

of the question.

A. Again, it's very difficult to give an answer that is true for every investigator for every clinical trial. I think if you speak to a specific clinical trial, usually power has an impact.

For example, in the MSI study record, like this is a trial that was designed to evaluate pembrolizumab in patients with microsatellite unstable tumors. The statistics that went into this trial would incorporate the power of whatever decision was ended up being discovered in the trial.

Q. When we talk about "power," what does that mean?

A. Power is a statistical term, and it generally describes the likelihood that the response that you receive is actually an accurate response, and you can have basically a false negative, missed true answer.

Q. And is it possible to design a clinical trial powered to one patient?

A. I'm not sure.

Q. So if you would, Dr. Oberstein, in

your declaration, back to Paragraph 10, so in the first sentence you say: My research activities that have focused on designing and conducting clinical trials is a novel agents, including immunotherapies for the treatment of colorectal and pancreatic and other GI cancer patients.

What do you mean by "immunotherapies"?

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

Q. Okay.

A. And so it can incorporate checkpoint therapies, other checkpoints besides the PD-1, PD-L1 that are well-known.

We also, as I said earlier, are doing studies that are called myeloid checkpoints essentially or myeloid immune suppressive cells. I am doing some studies with vaccines, and I'm looking at other components of the immune system.

Just to add one last detail: I'm

actually doing a trial now where we're having patients exercise to see if that enhances their immune system.

Q. Interesting.

A. So in theory, that counts as immunotherapy.

Q. So immunotherapy is a category that encompasses checkpoint inhibitors, monoclonal antibodies, vaccines, and even exercise?

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

A. So, again, like I said before, it really depends on the context and how someone is using it.

Q. Uh-huh.

A. And there are certainly very specific understandings within the literature where someone meets it one way or the other, I think a person of ordinary skill would have to evaluate each reference in its context.

Q. Okay. You mentioned immune checkpoint inhibitors. How many different types of immune checkpoint inhibitors are used in immunotherapy for oncology?

A. So I don't think I'm qualified to speak about all oncology. There are many, many cancers that are outside of my expertise.

Q. Uh-huh.

A. Within GI cancers, we primarily use two checkpoints right now, CTLA4 and PD-1. There are many ways to target those checkpoints, so there are multiple different drugs. Those are the two that are currently approved for GI cancers.

Q. Are --

A. There are other checkpoints in other cancers and there are many clinical trials looking at other points.

Q. And do you have some examples of those other checkpoints inhibitors that are used in other cancers?

A. So LAG-3 is one of the examples.

Q. Uh-huh.

Are PD-L1 checkpoint inhibitors available?

A. Yes.

Q. Okay. Are there any other types of checkpoint inhibitors that are available that

you're aware of?

A. So I'm not aware of any others that are FDA approved. Again, there are many in clinical trials that I can't necessarily comment on or remember today.

Q. Okay. Is T-cell transfer considered a type of immunotherapy?

A. So, again, this falls into the categories of how you define things.

Q. Uh-huh.

A. It depends on what the context is.

Q. Uh-huh.

A. So it certainly is not a checkpoint blockade and nothing to do with that checkpoint part of the immune system.

Q. Uh-huh.

A. It -- certainly T-cells are part of the immune system, and by giving activated T-cells, which is one way of T-cell transfer, you can stimulate the immune system.

Q. Is T-cell transfer a therapy that is used in oncology?

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

Q. Uh-huh.

A. There are others.

Q. Is oncolytic virus therapy considered a type of immunotherapy that's used in oncology?

A. So oncolytic virus therapy, if it's meant to stimulate the immune system, certainly could be considered a type of immunotherapy.

Q. And is that used in GI cancers?

A. It is not. Outside of clinical trials.

Q. Okay. But you're aware of oncolytic virus therapy being used in clinical trials for GI cancers?

A. I'm aware of one trial that I participated in that we utilized oncolytic virus therapy in pancreatic cancer.

Q. Are -- immune system modulators, are those considered immunotherapies for oncology?

A. So, again, immunomodulators could be a type of immunotherapy.

Q. And in the category of immune

system modulators, that can include cytokines; correct?

A. Cytokines, yes.

Q. Okay. And cytokines include interferons and interleukins?

A. Among many others, yeah.

Q. How many cytokines are available for oncology therapy?

A. So none of these are approved for GI cancers.

So I don't have a specific answer for you. There are many, many cytokines that are potential targets for cancer therapy.

Q. Okay. Is BCG also a type of immune system modulator?

A. Yes.

Q. Okay. And that is Bacillus Calmette-Guerin?

A. I don't think anyone has ever said something besides BCG.

Q. And what is BCG?

A. BCG is a -- essentially a live virus that is injected -- or bacteria, sorry, that's injected to stimulate an immune -- an

immune response and it's utilized in nonGI cancers.

Q. What about immunomodulatory drugs, are those a type of immunotherapy?

A. So anything that modulates the immune system is, and again, they're not utilized generally in GI cancers. And for the most part, they're not used in cancers. They're used in other diseases. Well out of the scope of my expertise for the record.

Q. Yeah.

Would VEGF inhibitors be considered an immunomodulatory drug?

A. So I listed them early as monoclonal antibiotics, as you recall. So generally, we would not consider them immunomodulatory.

As you detailed before in Exhibit 2405, that was one of the hypotheses of our study, is that they might have that role.

As you said, we really weren't able to conclude that, and so we don't know for sure.

THE WITNESS: Break?

ATTORNEY RATLIFF: Sure, Doctor. Want to break for lunch?

THE WITNESS: Good time for a break for lunch I think? We've been going for an hour.

ATTORNEY BROWN-MARSHALL: Actually, I may have one or two more questions.

ATTORNEY RATLIFF: It's up to you, Doctor.

THE WITNESS: It's okay with me to do one or two more.

BY ATTORNEY BROWN-MARSHALL:

Q. So, Dr. Oberstein, would you agree with me that the term "immunotherapy" covers a broader range of treatments than just immune checkpoint inhibitors; correct?

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

A. So as I've said several times, I think the term depends on the context in which it's used in a specific setting.

Within a sentence, within a context to a person of ordinary skill, it might mean they currently used immunotherapies, which are

primarily checkpoint blockade. It could mean something different, but it all depends on the context in which that word is used.

Q. So you would look to the context surrounding the word to understand what the term "immunotherapy" would mean?

A. I would do more than that. I would look to the context surrounding the word and what the person reading that word knows about the field of treatment and immunotherapy at the time that they're reading that, which could change over time.

Q. What was the understanding of the term "immunotherapy" in 2015?

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

A. So I think it would depend on the context. I think as of -- if we're talking about our critical date of July 10, 2015, you know, a person of ordinary skill looking through the MSI study record would already understand that checkpoint blockade therapy has been effective for a single patient with

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.

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

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A F T E R N O O N S E S S I O N

(1:01 p.m.)

CERTIFIED STENOGRAPHER: Back on the stenographic record at 1:01 p.m.

BY ATTORNEY BROWN-MARSHALL:

Q. Welcome back, Dr. Oberstein.

A. Thank you.

Q. Dr. Oberstein, have you ever participated in an investigator initiated clinical trial?

A. Can you clarify what you mean by that term?

Q. Well, are you familiar with the term "investigator initiated clinical trial"?

A. So I have used the term before, but I think there are many ways or multiple ways to use the term.

Q. I see.

What is your understanding of what the term means?

A. So, I mean, the words themself mean that the investigator or one of the investigators of the trial initiated that trial, but that could range from the

investigator coming up with an idea and then another company sponsoring it and others participating or them running the trial completely on their own or something well in between those two things.

Q. Have any of the clinical trials that you've been participated in been described as an investigator initiated clinical trial?

A. So, yes.

Q. Okay. And were any of these investigator initiated clinical trials related to pembrolizumab?

A. Yes.

Q. And were you the principal investigator on any of those investigator initiated clinical trials that involved pembrolizumab?

A. So for some of them, yes, for at least a period of time.

Q. Okay. And did you design those trials of pembrolizumab that were investigator initiated clinical trials?

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.

Q. And did they provide funding at the beginning of that investigator initiated clinical trial?

A. They provided a commitment for funding before the study opened.

Q. In your experience, how common are investigator initiated clinical trials?

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

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

Q. How frequently do they happen?

ATTORNEY RATLIFF: The same objection.

A. I can't report the frequency of those trials.

Q. Uh-huh.

A. They're not uncommon, but I don't know what percentages of trials are investigator initiated.

Q. When it comes time for FDA approval based on the clinical trial, do pharma companies use the data that was acquired during the investigator initiated clinical trial?

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

A. So I'm not very familiar with the pharma companies' submissions to the FDA, on what data they include in that.

Q. If you would turn to Paragraph 11 of your declaration.

And in Paragraph 11 you write: Currently, I am the site principal investigator on three active clinical studies involving metastatic colorectal cancer patients and two active clinical studies involving PD-1 inhibitors, including pembrolizumab.

Do you see that?

A. Yes.

Q. Okay. What three active clinical studies are you involved in regarding metastatic colorectal cancer?

A. So that might be an undercount, but one of the trials I'm looking at is using the medication called amivantamab and it is evaluating the use in -- there is actually three different trials that we're doing with

amivantamab looking at its use with metastatic colorectal cancer.

Q. And I'm sure I'm going to butcher this, amivantamab?

A. Amivantamab.

Q. Amivantamab, is that a monoclonal antibody?

A. It is a bispecific antibody essentially.

Q. And would you consider that an immunotherapy?

A. No.

Q. No? Why not?

A. It doesn't target the immune system.

Q. What about the second active clinical study involving metastatic colorectal cancer patients?

A. So actually just to clarify, I'm working on three clinical trials in metastatic colorectal cancer with amivantamab.

Q. Oh, okay. So all three are on --

A. But there are additional trials.

- - -

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

- - -

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

A. So I am participating in three active clinical trials utilizing amivantamab in metastatic colorectal cancer. In addition, I'm involved in other trials looking at metastatic colorectal cancer, including a clinical trial for medication called a KRAS inhibitor, which is RMC9805. It's a small molecule inhibitor of KRAS.

Q. Is that all of the clinical studies that you're involved in that involve metastatic colorectal cancer?

A. No. So I'm involved in additional studies that I'm either not the principal investigator or might be at some stages of closing.

Q. And do any of those additional studies involve using immunotherapies to treat 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

colorectal cancer. Again, it's not really an active trial, it is completed, but we haven't published the results yet, and we're still monitoring patients.

Q. And does that vaccine trial in metastatic colorectal cancer, does that involve investigators from Johns Hopkins University?

A. I don't believe so, but I can't be certain about all the investigators.

Q. So, Dr. Oberstein, if you would look at the last sentence in Paragraph 11, you say: I have received more than $4.5 million in funding in various pharmaceutical companies related to my research activities.

Do you see that?

A. Yes, I do.

Q. And how do you use those $4.5 million in funding for research activities? What does that go to?

A. So let me just clarify where that number comes from I think.

I don't actually keep track of every budget for every clinical trial. We

have an office that does that.

Q. Uh-huh.

A. And all of that money goes to support our clinical trial infrastructure and running the clinical trials.

That number that we actually -- that I put down, 4.5 million, comes from a federal website that collects information about pharmaceutical sponsorship to investigators for clinical trials that goes back around five years, so that number is over the last five years or so, maybe six, but most recent years.

Q. Okay.

A. And to answer the question, that money all goes to the university or the hospital and they utilize it to fund and operate the trials.

Q. And did some of that $4.5 million in funding come from Merck?

A. I would suspect so over the last six years, yes.

Q. Okay. And approximately what percentage of that $4.5 million came from

Merck?

A. I can't answer that. I'm not sure.

ATTORNEY BROWN-MARSHALL: I'd like to mark this as Exhibit 2408. Oh, 2407.

- - -

(Whereupon, document entitled Paul E. Oberstein | OpenPayments, is received and marked as Exhibit 2407 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2407.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, are you familiar with this document?

ATTORNEY RATLIFF: And I object to Exhibit 2407 for purposes of authentication, foundation, and hearsay.

A. I've never seen this printing of it before, but I'm familiar with the website OpenPaymentsData.cms.gov.

Q. Okay. And is that the website that you were mentioning about a government website that keeps track of funding for research and other purposes that physicians receive?

A. Yes.

Q. Okay. And this is the entry from OpenPaymentsData.cms.gov related to you; correct?

A. Correct.

Q. Okay. If you'd turn to the second page, there is a chart in the middle, and you see that according to this website, you received approximately $4.5 million in associated research funding; is that correct?

A. That is correct, and like I said before, that money doesn't go to me. It goes to the university that operates the clinical trials.

Q. Okay. And then you see at the top of that chart, there is an entry for general payment record.

Do you see that?

A. Yes.

Q. Okay. What are general payments?

A. So generally, general payments I think refer to either consulting compensation or fees for travel or other compensation to support an individual.

Q. And according to this website, you

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

contributor to your research; correct?

A. So I don't think that's accurate, but on this chart that's what's reported.

Q. Okay. So you don't think that the government payment system has the correct -- let me finish my question, has the correct monetary value for contributions to your research?

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

A. So I think that there is not standardization about how these payments are reported, and I don't -- and it's self-reported by companies, not by the government. So I don't think it reflects the entirety of the research payments that I've received or have been received for trials that I was affiliated with over this time period.

Q. But do you question the fact that you've received over $2.25 million in funding from Merck?

A. I do not question that.

Q. So when you receive research

funding from Merck, are those funds provided under some sort of agreement?

A. What do you mean by that?

Q. Do you have an agreement with Merck that governs the payment of research funding that you've received from Merck?

A. You mean me, personally, or the institution that I work for?

Q. Either one?

A. So I don't personally receive any research funding from Merck. None of this money goes to me and none of it is an agreement that I have. The institution that I work for, either Columbia, which is where a lot of this came to, or NYU have research agreements, clinical trial agreements with pharmaceutical companies.

Q. Including Merck?

A. Including Merck.

Q. Do you or your university keep records of payments that are received from Merck in relation to clinical trial research?

A. I do not keep record of those payments. I can't speak for my university.

Q. Aside from research funding, do you have any other relationships with Merck?

A. What do you mean by "relationships"?

Q. Do you serve on any advisory boards for Merck?

A. So in the past, I served on advisory board for Merck. I don't think I actually am currently, but it's sometimes hard to know if it's a one-time thing, whether it will happen again.

Q. And what was that advisory board related to?

A. So in I think 2017 to around 2020, I was on a gastric cancer advisory board for Merck.

Q. And did that involve pembrolizumab or Keytruda?

A. I mean, it was for Merck. It involved anything that Merck wanted to discuss with the advisory board for gastric cancer.

Q. Have you been a sponsored speaker on behalf of Merck?

A. I don't recall that, but I can't

recall every single speakership I've done.

Q. Have you received any travel funds from Merck?

A. So certainly associated with the advisory board that I was on, there would have been travel funds that went along with that.

Q. Have you received travel funds from Merck related to any other purpose?

A. Such as?

Q. Speaking at a conference?

A. I don't think so.

Q. Have you received any honoraria from Merck?

A. Outside of the context of being on an advisory board?

Q. Yes.

A. I don't think I've received anything outside of our advisory board agreements.

Q. And did you receive an honoraria as part of being on the advisory board?

A. So generally, you're compensated for being part of an advisory board, either on 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?

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

conference?

A. Yes.

Q. And were any of those presentations late-breaking presentations?

A. I don't recall right now.

Q. Do you usually attend ASCO?

A. What do you mean by "usually"?

Q. How often do you attend ASCO?

A. Most years I attend ASCO, unless there is some reason why I can't or it gets canceled.

Q. And did you attend Dr. Le's presentation at the 2015 ASCO conference?

A. So I don't have any specific recollection of attending that presentation.

Q. So, Dr. Oberstein, looking back to your declaration, in your declaration, you don't provide any opinions on anticipation; is that correct?

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

A. So in my declaration, I was asked to serve as an expert consultant for the '393

patent from the perspective of person of ordinary skill as of July 10, 2015, and I did that. And I think applying that perspective, I found and noted that all the claims of the '393 patent were taught or suggested by the MSI-high study record alone and with various prior art references.

Q. So you provide the opinion that they were taught or suggested, but you don't provide an opinion that they were anticipated?

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

A. So I did not say that. I found that all of the -- each and every claim limitation in the '393 patent was taught in the MSI-high study record and with various prior art references.

Q. But you don't provide an opinion that those claims were anticipated by the MSI-high study record?

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

Q. And what you're calling your primary finding does not contain the word "obviousness"; correct?

A. So I'll say it again. I think that it's my opinion that each and every claim limitation of the '393 patent is taught in the MSI-high study record alone and in combination with prior art references for a person of ordinary skill in the art as of July 10, 2015.

Q. And when you said that, you did not use the word "obvious"; correct?

A. Correct.

Q. And in your declaration, you do not provide opinions on nexus; is that correct?

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

A. So in my declaration, I provide in .12 a discussion about secondary considerations alleged by JHU and find that they were fundamentally flawed, as I detailed, because many of them refer to publications that were not evaluated at the critical date of July 10, 2015, and thus I think they're

flawed in their presentation.

Q. But as part of your analysis in .12, you did not provide a nexus analysis; correct?

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

A. So my analysis in .12 is that the secondary considerations are flawed and that they are not applicable as of the critical date of July 10, 2015.

Q. And your .12 does not use the word "nexus"; correct?

A. My finding in .12 is that the secondary considerations are fundamentally flawed as of the date of July 10, 2015, and thus don't form the basis for further argument.

Q. And that does not contain the word "nexus"; correct?

A. Correct.

Q. So if you look at Header Number 7 in your table of contents, you say: The claims of the '393 patent are taught or

suggested by the prior art.

What does it mean for the prior art to teach or suggest the claims of the '393 patent?

A. I'm not sure I understand the question.

Q. Well, you wrote the words: The claims of the '393 patent are taught or suggested by the prior art; correct?

A. I did write those words, yes.

Q. Okay. What does it mean for the claims of the '393 patent to be taught or suggested by the prior art?

A. It means that the prior art contains the claims of the '393 patent from the perspective of a person of ordinary skill evaluating the prior art on July 10, 2015.

Q. What's the difference between teaching and suggesting?

A. So some -- I would say teaching refers to things that are said explicitly and suggestion are things that are implicit.

Q. And how did you assess whether the prior art taught claims of the '393 patent?

A. I'm sorry, can you repeat that?

Q. How did you assess whether the prior art taught the claims of the '393 patent?

A. I utilized a perspective of a person of ordinary skill and the available prior art as of July 10, 2015, analyzed the claims in the '393 patent and then determined or looked to see whether they were taught in the prior art.

Q. How did you assess whether the prior art suggested the claims of the '393 patent?

A. So in the same way I looked at the claims in the '393 patent and what was reported in the prior art as of July 10, 2015, and using the perspective of a person of ordinary skill, determined what would be suggested by what was written in the prior art.

Q. In your declaration, do you provide an opinion on reasonable expectation of success?

A. Sorry. Could you repeat the

question?

Q. In your declaration, do you provide an opinion on reasonable expectation of success?

A. I'm sorry, what do you mean by "an opinion on reasonable expectation of success"?

Q. So maybe it will help to look at an example. Can you go to Page 68 of 102.

A. Yes, I'm there.

Q. Okay. Oh, I'm sorry, Page 59 of 102.

A. Yes.

Q. And you see at the very bottom and continuing onto the next page it says: Additional Dr. Neugut explains that the state of the art known to the POSA as of July 10, 2015 --

A. I'm sorry, I don't think I have the right page.

I've got it now. Thank you.

Q. Got it.

July 10, 2015, would counsel the POSA to carry out the methods of treatment found in the MSI-high study record with a

reasonable expectation of success.

Do you see that?

A. I do see that, yes.

Q. Okay. So you're providing opinions on reasonable expectation of success?

A. So I'm providing an opinion that a POSA would be motivated to carry out the clinical trial described in the MSI-high study record with a reasonable expectation of success.

Q. And you agree with Dr. Neugut on that point; correct?

A. I'm not sure what you mean by that.

Q. So you say that Dr. Neugut explains the state of the art known to a POSA as of July 10 would counsel the POSA to carry out the methods of treatment found in the MSI-high study record with a reasonable expectation of success.

Do you agree with that statement?

A. So, yes, I agree with Dr. Neugut, that the state of the art at the relevant time of July 10, 2015 would motivate a POSA to carry out the methods of treatment found in

the study record with a reasonable expectation of success, because as I state, the POSA would have known that physicians had successfully treated a colorectal cancer patient who was MSI-high with a PD-1 inhibitor with a complete response and that pembrolizumab was approved for another oncology indication prior to that date.

Q. Did you apply the same standard for reasonable expectation of success that Dr. Neugut applied?

A. I don't know what Dr. Neugut's reasonable expectation of success standard is, but I utilized my standard in independently evaluating what a POSA would have done at that time.

Q. Okay. And what was your standard that you apply for reasonable expectation of success?

A. So the standard I utilized is whether a person of ordinary skill, who was familiar with the prior art and knew about success of treating MSI-high colon cancer in one patient and the success of pembrolizumab

in other cancers, would be motivated to treat a patient according to the method described in the MSI study record and expect that that would provide benefit for the patient over not doing that.

Q. When you say "treat a patient according to the method described in the MSI-high study record," is that patient MSI-high or not?

A. So in my previous example, as I stated, I think a POSA would have been motivated to treat an MSI-high colorectal cancer patient with the method described in the MSI-high study record based on the knowledge at that time that a previous patient with MSI-high colon cancer had a complete response and that pembrolizumab is approved for other immunotherapy indications in cancer with a reasonable expectation of success for that patient.

Q. All right.

Dr. Oberstein, if you would turn to Paragraph 21 in your declaration.

And in Paragraph 21 you write: I

understand that JHU argues that the term "in response to" should be construed to mean in reaction to; correct?

A. That's correct.

Q. Okay. And you write further: I understand that the parties do not dispute that the term "in response to" requires causality; correct?

A. That's correct.

Q. Okay. Is Merck -- strike that.

Are you offering a construction of the term "in response to"?

A. That's different than what I write.

Q. Let's try it this way: What meaning of "in response to" did you apply in forming your opinions?

A. So as I wrote there, I understand that the parties do not dispute that the term "in response to" requires causality and that's what I utilized.

Q. So you are not using a construction of the term "in response to"; correct?

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

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?

A. So as I stated here, I went with

what I understand to be the opinion of both parties that the term "in response to" requires causality.

Q. Okay. So in forming your opinions, how did you assess causality with respect to the term "in response to"?

A. I'm sorry, I don't understand the question.

Q. So you said that you interpreted "in response to" as meaning in response to with a requirement that there be causality; correct?

A. Correct.

Q. Okay. How did you determine that there was causality with respect to the term "in response to"?

ATTORNEY RATLIFF: It's the same question. I object to the form of the question.

A. I still am not sure if you mean in the study record, in the patent, in the --

Q. What does it mean that "in response to" requires causality?

A. It means that the action is taken

in response to the first finding.

Q. How did you determine that a given action was taken in response to with causality?

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

A. So I don't understand the question, but let me go back to my finding, which is that in the ClinicalTrials.gov study record, which was available to a person of ordinary skill as of July 10, 2015, there is a cohort of patients who are required to be enrolled with MSI positive colorectal cancer.

Q. Uh-huh.

A. So I think a person of ordinary skill reading that requirement would understand that in order to be enrolled in this study and receive treatment in that arm, a subject would have to have MSI-high colorectal cancer and then be treated with an effective dose of pembrolizumab after determining that fact.

Q. So the evidence of causality that you're relying on is the fact that Arm 1

described in what you call the MSI-high study record includes only MSI-high colorectal cancer patients?

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

A. So I'm stating that in the MSI study record, MSI-high study record, Arm 1 describes treating a patient who is MSI positive colorectal cancer with an effective dose of pembrolizumab based on their qualification in that arm as having MSI positive colorectal cancer.

Q. So the fact that the patients in Arm 1 were all MSI-high colorectal cancer patients indicates to you that there was causality with treating those patients with pembrolizumab in response to determining that they are MSI-high?

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

A. So the fact that that is an inclusion criteria and required in order for a patient to be treated on a trial in that arm

means that they have to have that qualification in order to be treated on the trial.

Q. And you don't rely on any other evidence in the MSI-high study record to indicate the causality associated with treating in response to determining the patient is MSI-high?

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

A. So I rely on the information, which I just described to you, which I think is sufficient to indicate causality in Arm 1 for patients with MSI-high colorectal cancer being treated with an effective dose of pembrolizumab in response to being MSI-high.

Q. Did Merck inform you that they have previously argued that "in response to" means "as the reaction specifically to"?

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

A. Sorry. Can you repeat the

question?

Q. Did Merck inform you that they have previously argued that "in response to" means "as the reaction specifically to"?

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

A. So I'm not sure if you're suggesting that's different than what I wrote here, which is that the parties do not dispute that the term "in response to" requires causality. That is what I was communicated by Merck. That's what I put in my declaration.

Q. So your construction or the meaning that you utilize for "in response to" is consistent with "as the reaction specifically to"?

A. Again, I'm not sure what you're trying to clear with those words. Is that different than causality? That's what I used.

Q. You tell me.

A. So I understand that the parties do not dispute that the term "in response to" requires causality, and that is what I adopted

and included in my opinion.

Q. If you had used the construction "as the reaction specifically to," would that change your opinion?

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

A. I am not sure. I have to reconsider. In that light, that's not what I used.

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

If you would, let's go to Paragraph 23. And you say: I understand the POSA for purposes of my analysis of the '393 patent is an oncologist or a medical professional in a related field with at least five years of experience with treating cancer patients; correct?

A. That's correct.

Q. Okay. And what is the source of that understanding of a definition of a POSA?

A. You're asking me where did I get that definition from?

Q. Uh-huh.

A. So I saw that definition in

Dr. Neugut's declaration, and then I was advised by my counsel to utilize that definition in preparing my assessment.

Q. Okay. What do you mean by a medical professional in a related field?

A. So not only oncologists. There are other people who can treat cancer patients, like nurse practitioners or related radiation oncologist who I think would be appropriate as a POSA.

Q. So you think a nurse practitioner would qualify as a POSA under Merck's definition?

A. It depends on who they were and if they are a medical professional treating cancer patients.

Q. Okay. In Paragraph 24 you write: I disagree with JHU's definition for the POSA given that the '393 patent relates to cancer therapy and provides a method of treating a cancer patient; is that correct?

A. That is correct.

Q. Okay. So you also assessed JHU's definition of the POSA; correct?

A. By "assess," do you mean did I review it?

Q. Well, you disagree with their definition; correct?

A. Correct.

Q. So you must have determined that there is something wrong with their definition?

A. Correct.

Q. Okay. And how did you assess JHU's definition of a POSA?

A. Again, I'm not sure I understand. What method did I use to assess it?

Q. Are there certain requirements of a POSA that you feel like JHU's definition did not meet?

A. So, as I stated here, I disagree with JHU's definition for the POSA because the patent is essentially a cancer therapy patent, so it's a method to give a cancer therapy to patients and it provides a method of treating an actual cancer patient, which is why I think it's not correct to involve someone as a POSA who doesn't have an active role in treating

cancer patients and providing this therapy to patients.

Q. So in your understanding, a POSA is someone who is actively using the method of a claim?

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

A. I think a POSA is a person who would be able to appreciate the aspects of the claim and that will be able to assess them.

Q. And where did that understanding come from?

A. That is the understanding that I think I received from my counsel, but I can't say exactly.

Q. And in your opinion, someone who understands the steps of a claimed method of treatment would qualify as a POSA; correct?

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

A. Could you repeat the question? Sorry?

Q. So in your opinion, someone who

understands the steps of a claimed method of treatment would qualify as a POSA?

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

A. So I don't think understanding the steps alone would qualify a person as a POSA. They'd also have to have some knowledge and experience in applying the methods described in the claims.

Q. Uh-huh.

A. In this case, a method of providing cancer therapy and treating a cancer patient.

Q. Did you determine whether Merck's definition of the POSA would exclude any of the inventors on the '393 patent?

A. I did not determine that.

Q. Okay. Why not?

A. I don't think that was relevant to my assessment and analysis here.

Q. Okay. So the inventors on a patent are not relevant to the assessment of a person of ordinary skill with respect to that patent?

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.

Q. So it's okay for the definition of a person of ordinary skill to exclude some inventors in your opinion?

ATTORNEY RATLIFF: And the inventors you're talking about are inventors that are corrected on the patent or --

ATTORNEY BROWN-MARSHALL: Counsel, that's enough with the speaking objections. I'll ask the questions --

ATTORNEY RATLIFF: That wasn't an objection. It's a clarification to your question.

ATTORNEY BROWN-MARSHALL: That is a speaking objection.

ATTORNEY RATLIFF: It's not an objection. If you don't want to respond to my question, then I object to the form of your question.

A. So I don't think it's irrelevant, but I don't think that a person in order to be defined as a POSA has to be suitable to be the inventor of the patent.

BY ATTORNEY BROWN-MARSHALL:

Q. And I'm not asking whether they're

suitable. I'm saying if your definition of a POSA excludes inventors, is that an acceptable definition of a POSA?

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

A. So I'm not sure.

Q. Okay. And in Paragraph 25 you say: All of my opinions expressed in this declaration are from this perspective of the POSA as of the critical date of the '393 patent.

What do you mean by "this perspective of the POSA"?

A. So I defined in Paragraph 23 that I understand the POSA is an oncologist or a medical professional in a related field with at least five years of experience treating cancer patients.

The POSA would also have experience in or access to a person with knowledge of clinical trials for therapeutics and how they work, as well as experience with or access to a pathologist with comparable experience.

Q. Dr. Oberstein, if you would turn to

Exhibit 1005. I believe you have a copy in front of you.

ATTORNEY BROWN-MARSHALL: Mark this as Exhibit 1005.

- - -

(Whereupon, document MERCK EX1005, is received and marked as Exhibit 1005 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 1005.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, we've talked about this exhibit previously. This is the June 10, 2013 submission to ClinicalTrials.gov; correct?

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

A. That is correct.

Q. And this ClinicalTrials.gov submission is related to the Clinical Trial Number NCT01876511; correct?

A. That is correct.

Q. And did you participate in that clinical trial?

A. No, I did not.

Q. So you didn't have any patients enrolled in that study?

A. No, I did not.

Q. And if you look starting on Page 1 and continuing on to Page 2, there is a list of 28 submissions to ClinicalTrials.gov; correct?

A. That is correct.

Q. And it's your understanding that all 28 of those submissions are related to Clinical Trial Number NCT01876511?

A. I would assume that, but I have not reviewed all 28 of those submissions.

Q. Okay. How many of those submissions did you review?

A. I don't recall. I definitely reviewed more than one, but I don't recall if I reviewed more than two or three.

Q. Okay. And which additional two or three submissions did you review?

A. So I recall reviewing probably the one dated June 9, 2015, or Version 11 because that was the one that was closest to the

critical date of the patent of July 10, 2015.

Q. Uh-huh.

A. I don't recall if I looked at other ones as well.

Q. Okay. But you don't rely on that June 9, 2015 submission in your declaration; correct?

A. That is correct. I rely on the one in front of us.

Q. If you would turn to Page 5 of the exhibit. And you see about two-thirds of the way down under eligibility there is a category: Criteria, inclusion criteria.

Do you see that?

A. Yes, I see that.

Q. Okay. What is the purpose of inclusion criteria in a clinical trial?

A. As the name implies, inclusion criteria is something that is necessary to be accurate to be included in the clinical trial.

Q. And looking at the inclusion criteria in this exhibit, nothing in those inclusion criteria requires that the patients have a certain stage of cancer; correct?

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

A. So I don't think anything in the inclusion criteria says about the stage of cancer, but a person of ordinary skill in the art would understand that if a patient is going on a clinical trial, it would only be appropriate at that time when they're evaluating this clinical trial record to be a person who has metastatic or incurable colorectal cancer and has already progressed on one or two lines of therapy, specifically two lines if possible, before it would be appropriate to go on a clinical trial as recommended in ClinicalTrials.gov.

Q. So it's your opinion that there are additional inclusion criteria that are unstated in this MSI -- what you called the MSI-high studied record?

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

A. So I'm not sure what you mean by "inclusion criteria." I think that a person of ordinary skill reading this study record

would understand a certain thing about the MSI positive colorectal cancer and would understand that it's only appropriate for that person to go on a trial if they have metastatic disease and have progressed in prior therapy.

Q. The people reading these submissions on ClinicalTrials.gov, they're not limited to what you define as a person of ordinary skill in the art; correct?

A. That is correct. This is an open document. Anyone can read it.

Q. Okay. So for a colorectal cancer patient reading the MSI-high study record, they're going to look at these inclusion criteria and they're going to think, Well, it doesn't say that I have to be Stage 4, I'm Stage 2, I could potentially enroll; correct?

A. Is that a question?

ATTORNEY RATLIFF: I object. It sounds like it is a question. I object to the form of the question, if it is a question.

A. So I don't really know what a patient or someone else looking at this would

say. I evaluated this and reported on this from the perspective of a person of ordinary skill in the art as of July 10, 2015, and at that time, a POSA would have looked at this and said, If this clinical trial is being tested in MSI positive colorectal cancer, that's referring to a patient who has advanced disease and has failed prior therapy.

Q. Even though that's not explicitly stated in the inclusion criteria?

ATTORNEY RATLIFF: Hold on.

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

A. I think that would be obvious to a POSA looking at this document.

Q. And there is nothing in the inclusion criteria that explicitly requires prior therapy; correct?

A. As I just stated, there is nothing that explicitly says one or two prior therapies are needed, but a POSA looking at a study of a novel therapy in MSI positive colorectal cancer would understand and know that this person has to have advanced

incurable disease and have progressed from prior therapy.

Q. In your clinical trials that you've conducted, if prior therapy is required for a patient to enroll, have you explicitly stated that in the inclusion criteria?

A. I don't recall specifically. I'd have to look at those references to answer that.

Q. Have you -- in the clinical trials that you have designed, have you ever assumed that doctors would understand what your inclusion criteria are even if you don't list them?

A. I've used different standards I would say in submitting information, but absolutely understand that someone else reading this has to have some knowledge in order to interpret it, in light of what they're going to be using it for, and it would be very customary to rely on an outside expert or, sorry, an outside POSA to evaluate what I'm writing in ClinicalTrials.gov posting.

Q. Can you identify any clinical trial

that you've conducted in which metastatic cancer was a requirement in which you haven't explicitly written that in the inclusion criteria?

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

A. You mean the inclusion criteria on ClinicalTrials.gov

Q. Yes.

A. So I've not reviewed my postings and I can't tell you whether that has occurred or not occurred.

Q. Would you be comfortable with a ClinicalTrials.gov submission for a clinical trial that required patients that have metastatic cancer, but does not specifically include metastatic cancer in the inclusion criteria?

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

A. What do you mean by "comfortable"?

Q. Well, you previously testified that you review and sign off on the ClinicalTrials.gov submissions for your

clinical trials; correct?

A. That is correct.

Q. Okay. If you were conducting a clinical trial in which metastatic cancer was required for enrollment, would you be comfortable signing off on the ClinicalTrials.gov submission that did not list metastatic cancer in the inclusion criteria?

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

A. So it's a theoretical question and I'm not 100 percent sure what I would do in the real moment, but I would be very confident that anyone with experience treating colorectal cancer patients, who is interested in putting a patient on the trial, learning about the trial, would understand from this description that this is relevant for a patient with advanced cancer who has failed prior chemotherapy.

ATTORNEY RATLIFF: And I'll just note for the record that when Dr. Oberstein said "this description," he was pointing with his

fingers to Exhibit 1005.

Q. Is it your opinion that if a colorectal cancer patient who was not metastatic would be excluded from this clinical trial based on Exhibit 1005?

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

A. So I don't think that Exhibit 1005 is an exhaustive list of inclusion and exclusion criteria for a specific patient, but I think that a person of ordinary skill in the arts reading this clinical trial would not expect that they would be able to enroll a nonmetastatic patient who had not failed prior chemotherapy.

Q. You say that they would not expect that a patient with nonmetastatic colorectal cancer would be able to enroll in a study that was proposed by Exhibit 1005, but would they understand that that patient would necessarily be excluded?

A. So I think a POSA would understand that that patient would be excluded based on the fact that it is not standard of care and

was not at that time to enroll a patient in experimental clinic trial if they have metastatic colorectal cancer and have not received two lines of therapy or if they're nonmetastatic and they could be cured by surgery, the standard of care would be to take them to surgery to remove their tumor.

Q. Are there nonmetastatic colorectal cancers that cannot be cured by surgery?

A. So there are times where colorectal cancer can grow locally to such an extent that either it can't be cured by surgery or the person is too sick and, therefore, they can't undergo surgery.

Q. And I think you used the term locally advanced cancer in your declaration to describe those types of cancers; correct?

A. That is correct.

Q. Okay. So would a treating oncologist who has a colorectal cancer patient with locally advanced colorectal cancer expect their patient to be excluded from the clinical trial proposed by Exhibit 1005?

ATTORNEY RATLIFF: I object to the form

of the question.

A. So that's a much more complicated group of patients, because a lot of it depends on other factors. I think if you look at the treatment guidelines, which we have from the NCCN, they group together in many ways locally advanced unreceptible patients and metastatic patients. They're not -- excuse me, as I said earlier, the exact same patient population. There are other factors, including whether a patient has measurable disease, based on whether they have something that can be measured on a CAT scan or by actual measurements.

Q. So there is some group of nonmetastatic colorectal cancers that a person of ordinary skill would expect would be able to be enrolled in the clinical trial proposed by Exhibit 1005?

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

A. So I think that a person of ordinary skill would have to evaluate a

locally advanced nonmetastatic patient who has already received and progressed in prior therapy to determine if they would be suitable for the trial based on their other treatment options and whether this was possible.

Q. But there is nothing in Exhibit 1005 that excludes that nonmetastatic locally advanced colorectal cancer patient?

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

A. So there are other criteria, of course, in 1005 such as having measurable disease, but if the person met all the other criteria, this is not necessarily excluding them if they have received two lines of prior therapy and progressed, so just to add a little clarity there I think I can.

So in general when we talk about staging of colorectal cancer patients, if a person has cancer that is initially locally advanced and then it grows, it progresses on chemotherapy, we generally think of that as recurrent and, therefore, Stage 4 cancer or, quote/unquote, metastatic.

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

Q. In your opinion, would a colorectal cancer patient who had refused at least one prior therapy qualify for the clinical trial proposed by Exhibit 1005?

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

A. So I think that if a patient met the criteria in the NCCA guidelines for clinical trial evaluation, they would be appropriate for the trial, would be very unusual to enroll a patient in a trial with an experimental agent if we have effective chemotherapy for that patient.

If for some reason that patient cannot receive the chemotherapy, such as an allergy to the medication or some other disorder, then it would be reasonable to give them the next available therapy, which is a 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

criteria in Exhibit 1005 would not be excluded from this clinical trial if they had not received a prior therapy because of an allergy to the available chemotherapy?

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

A. So I don't think a POSA can determine if that person was excluded or based on what's available in 1005.

Q. Why not?

A. Because it does not speak to that point.

Q. Because it doesn't say anything about prior therapies?

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

A. So, again, a POSA reading this clinical trial report would understand that a patient with metastatic colorectal cancer is only appropriate for clinical trial based on current guideline or guidelines in July 2015 if they had failed first and second line chemotherapy options, which are standard and

life prolonging options. They would not have placed a person on a clinical trial such as this if they didn't fit that criteria.

Q. So what do the guidelines say about a colorectal cancer patient who those first and second-line therapies are not available to them because of let's say an allergy?

A. So I cannot think of an instance in which a patient can receive either of those chemotherapies because of an allergy. I think it's possible that a person would have an allergy to one of those medications and not be able to receive it, but the standard of care would be to give the medication that -- either a modified dose or some way to try to overcome that limitation. If there was absolutely no way to give the chemotherapy, then that person would be suitable for third line therapy because they didn't have a second line option.

Q. And that third line therapy would include clinical trials?

A. So according to the guidelines, it would include consideration of a clinical 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?

ATTORNEY RATLIFF: I object to the assumption that's leading up to this question.

A. I'm with you so far.

Q. Okay. You're with me?

A. Very hypothetical. Yes.

Q. Okay. So this hypothetical colorectal cancer patient's tumor is tested and they are determined to be MSI-high, would that patient be enrolled in Arm 1 of the proposed clinical trial?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the portion of the question illuminating the hypothetical parts of the question.

A. So can you tell me more about this hypothetical question -- patient, sorry? What age are they? What stage? What have they had prior treatment with?

Q. Let's just assume that all of those factors are such that they would qualify to be in the clinical trial. So let's assume the patient is qualified to be in the clinical trial, okay? That colorectal cancer patient is tested for MSI and tests positive for

MSI-high. They would be enrolled in Arm 1 of the clinical trial; correct?

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

A. So, again, I'm not following the exact patient we're talking about. So can you be a little clearer on what have they previously been treated with? What else do we know about them, etc.?

Q. So we don't need to know. They are otherwise qualified. Whatever the qualifications are, they've been enrolled in the study.

ATTORNEY RATLIFF: I object to this premise of we don't need to know.

Q. So let's assume that there is a colorectal cancer patient who has qualified and enrolled in the study proposed in Exhibit 1005, their colorectal cancer is tested and they are determined to be MSI-high, which arm would they be enrolled in?

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

A. I'm really not sure what you're

trying to say, but I don't think a patient could be enrolled in a trial without knowing what arm they'd be enrolled into. So you would need to have the MSI testing prior to enrolling them in the trial. So I'm not clear if you said that or not.

Q. Okay. So let's assume that you have a colorectal cancer patient who is MSI-high and who is enrolled in Arm 1 of the proposed clinical trial, how would that patient be treated?

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

A. So in the arms of intervention section of the clinical study record, it says that: Expect numbers, that the MSI positive colorectal cancer patient would be treated with NK3475, which is pembrolizumab, 10 milligrams per kilogram every 14 days.

Q. Let's assume that you have a colorectal cancer patient who is MS stable, so not MSI-high, and who is enrolled in Arm 2 of the proposed clinical trial, how would that patient be treated?

A. So in the same table, an MSI negative colorectal cancer patient would be treated with MK3475, 10 milligrams per kilogram every 14 times.

Q. And that's the same treatment as the MSI-high colorectal cancer patient enrolled in Arm 1; correct?

A. That is correct. It's called MSI positive in this table, but yes.

Q. And, Dr. Oberstein, in your declaration, you provide opinions regarding JHU's evidence of secondary consideration; is that correct?

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

A. I'm sorry, can you repeat the question?

Q. In your declaration, you provide opinions regarding JHU's evidence of secondary considerations; is that correct?

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

A. So I do provide opinions regarding JHU's alleged secondary considerations.

Q. Okay. What are secondary considerations?

A. I understand that secondary considerations are other things that might be included to look for obviousness of a patent claim, such as -- I don't recall what they are, but a skepticism about the claim treatment methods.

Q. So the secondary considerations that you evaluated were skepticism --

A. I evaluated all the ones they quoted. That's just the one that I mentioned first.

Q. And how did you evaluate the secondary considerations that you evaluated?

A. So as I detail, and I'm happy to go through all of them, JHU's experts raised several areas of secondary considerations. One of them was that people were skeptical about the claimed methods of treatment.

As I noted in Paragraph 180, I think that was a flawed comparison, of course,

because the critical time at which we're evaluating this '393 patent is July 10, 2015, and those discussions about skepticism that happened on a personal level were from a very different time period and were clearly not reported for July 2015.

Q. So you're of the opinion evidence of secondary considerations that is dated prior to the priority date is relevant?

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

A. That is not correct.

I think what's really important is what the person of ordinary skill in the art would have felt at the time of the priority date, and there is no evidence of skepticism at the time of the priority date.

On the contrary, there was a lot of enthusiasm about doing this research as evidenced by the fact that BMS and others had started their own clinical trials testing MSI-high colorectal cancer with PD-1 antibodies.

Q. As of July 10, 2015, were results

available for the BMS clinical trial testing MSI-high colorectal cancer that you mentioned?

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

Q. But that was a single patient; correct?

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

Q. And as of July 10, 2015, were any results available for the Merck clinical trial in MSI-high colorectal cancers that you mentioned?

A. Which Merck study? I'm sorry?

Q. Well, you cited a Merck study as evidence that there would not be skepticism; correct?

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?

A. That is correct.

Q. Does that date ring a bell for you?

A. No.

Q. No?

That's also the date that the results of the Hopkins trial that was proposed in Exhibit 1005 were publicly announced?

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

A. You mean the MSI-high study that we've been discussing?

Q. I mean, the clinical trial that's proposed in Exhibit 1005.

A. Correct.

Q. Okay. So the Merck trial was announced the same day that the Hopkins results were announced?

ATTORNEY RATLIFF: Wait. They're not Hopkins results.

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

A. So, again, I will restate it, but I agree that the date that the -- this MSI study results were initially announced was the same

date that Merck posted the second study on ClinicalTrials.gov.

Q. And that second study posted by Merck on ClinicalTrials.gov was a follow-up study to the clinical trial proposed in Exhibit 1005; correct?

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

A. What do you mean by a follow-up study?

Q. That Merck study that was proposed in Exhibit 1148 followed on the results of the Johns Hopkins study proposed in Exhibit 1005; correct?

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

A. So I don't know what motivation Merck had in doing that study or what they included in the submission. In Exhibit 1148 they proposed a study of the MSI-high colorectal cancer and proposed treating those patients with pembrolizumab.

ATTORNEY BROWN-MARSHALL: I'd like to mark as Exhibit 2061.

- - -

(Whereupon, Merck document JHU2061, is received and marked as Exhibit 2061 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2061.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, are you familiar with this exhibit?

ATTORNEY RATLIFF: And I'll object to Exhibit 2061 for the purposes of authentication, foundation, and hearsay.

A. I am not familiar with this press release.

Q. Okay. And does this appear to be a Merck news release, dated May 29, 2015?

A. Yes, it does.

Q. And do you see about two-thirds of the way down where it says: Merck, NYSE:MRK, known as MSD outside the United States and Canada, today announced results from the first study evaluating the correlation of benefit with an immunotherapy based on DNA mismatch repair, MMR, deficiency, a well-established

form of genetic instability in many cancers characterized by the loss of function of the MMR pathway.

Do you see that?

A. I do see that, yes.

Q. And then it says: The Phase II study led by researchers from Johns Hopkins Kimmel Cancer Center evaluated Merck's anti-PD-1 therapy, Keytruda pembrolizumab, in 48 valuable heavily pretreated patients with advanced colorectal cancer and other solid tumors.

Do you see that?

A. I do see that.

Q. And do you understand that this news release is referring to the results of the clinical trial proposed in Exhibit 1005?

A. Yes.

Q. And if you would turn to Page 2 and then the first full paragraph, do you see where it says: Based on the encouraging results of this early study, Merck will initiate a registration Phase II study Keynote 164 to evaluate the efficacy and safety of

Keytruda based on mismatch repair status and locally advanced unreceptible or metastatic Stage 4 colorectal cancers.

Do you see that?

ATTORNEY RATLIFF: You read that incorrectly. I object to the form of the question.

A. I do see that statement, that sentence.

Q. Okay. Is that Phase II study Keynote 164, is that the study proposed in Exhibit 1148 that you rely on?

A. Yes, it is.

Q. Okay. And the press release indicates that that study proposed in Exhibit 1148 is based on the encouraging results of this early study; correct?

A. The press release does say that, yes.

Q. And this early study that it's referring to is the study led by Johns Hopkins University proposed by Exhibit 1005; correct?

A. That's correct.

Q. Okay. And if you look at the next

paragraph, there is a quote from Dr. Roger Dansey, therapeutic area head and senior vice-president oncology, late stage development, Merck Research Laboratories.

Do you see that?

A. I see that.

Q. Okay. And Dr. Dansey says: These exciting results, while early, suggest that evidence of DNA mismatch repair deficiency may be an important way of identifying tumors that are responsive to checkpoint blockade.

Do you see that?

A. I see that.

Q. So Dr. Dansey didn't say that DNA mismatch repair deficiency is conclusively a way of identifying tumors that are responsive to checkpoint blockade; correct?

ATTORNEY RATLIFF: Are you asking about in this article or if he's ever said that?

ATTORNEY BROWN-MARSHALL: I'm asking about in this article.

A. So I didn't read the rest of the article. I'm just seeing this for the first time. The sentence you just read uses the

word "maybe."

Q. Maybe.

And Dr. Dansey goes on to say that: DNA mismatch repair deficiency is an established biomarker in many types of cancer, and these results open the door for research with Keytruda in colorectal cancer and other tumor types with this potentially clinical meaningful tool.

Do you see that?

A. I see that.

Q. So at this point on May 29, 2015, DNA mismatch repair deficiency is not an established biomarker for treatment with Keytruda in colorectal cancer; correct?

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

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

Q. Uh-huh.

A. Where does this indicate anything about whether Keytruda is an established biomarker for -- whether mismatch repair deficiency is an accomplished biomarker for treatment with Keytruda?

Q. Well, according to Dr. Dansey, DNA mismatch repair deficiency is a potentially clinically meaningful tool; correct?

A. Correct.

Q. And he goes on to say: We look forward to initiating a registration Phase II study of Keytruda in patients with colorectal cancer to further explore this genomic biomarker; correct?

ATTORNEY RATLIFF: You read that incorrectly. I object to the form of the question.

ATTORNEY BROWN-MARSHALL: Okay. I'll read it again.

Q. We look forward to initiating a registrational Phase II study of Keytruda in patients with colorectal cancer to further explore this genomic biomarker; correct?

A. That is what is written here, yes.

Q. Yes. He didn't say that they were applying for FDA approval for treating colorectal cancer based on DNA mismatch repair deficiency at this point; correct?

ATTORNEY RATLIFF: I object to the form

of the question.

A. He did not say that.

Q. He said: We'll be further exploring this genomic biomarker?

A. So, again, I did not conduct my analysis based on the date of May 29, 2015, but based on July 10, 2015, I concluded and stand by that a person of ordinary skill in the art would look at the available data, including the trial reports, trial records, the report of the one patient who succeeded, and would be motivated to conduct clinical trial -- conduct, sorry, therapy of a patient with MSI-high colorectal cancer with a reasonable expectation of success. I assume Dr. Dansey assumed that as well, but I do not speak from his perspective.

Q. Had the Merck trial proposed in Exhibit 1148 enrolled any patients as of July 10, 2015?

A. I don't know. I did not make any representations about enrollment on these trials.

Q. So it's just the initiation of that

trial described in Exhibit 1148 that you're relying on?

A. So I don't think I relied on the initiation either. I relied on the publication of the plan to do that trial, which would have been available to a person of ordinary skill in the arts and would have given that person motivation to conduct a trial according to what was described in the MSI study record, and to expect positive results if they follow the methods of this trial to achieve positive results from treatment of patients with MSI-high colorectal cancer with pembrolizumab.

Q. Did you investigate at all the status of Merck's trial proposed in Exhibit 1148 as of July 10, 2015?

A. Your question is did I investigate whether it was enrolling patients?

Q. The status?

A. I do not recall doing that. Again, the reason I reference that study and what reported from is that it was available publicly to a person of ordinary skill and

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?

A. Yes, I did.

Q. Okay. Did you review the exhibits that she cited in her declaration?

A. I believe so, but I might have to be refreshed on some of them.

Q. And you're engaged as an expert by Merck in this case; correct?

A. That is correct.

Q. And did you ask Merck when it first funded Dr. Le's study?

ATTORNEY RATLIFF: Object.

Hold on.

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

A. I did not.

Q. Okay. Do you believe Merck would have kept records of any funding that it provided for Dr. Le's study?

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

A. So I'm really not familiar with how Merck keeps records.

Q. Uh-huh.

A. I don't know how long they retain

them or where those things are.

Q. Uh-huh.

A. So I'm familiar with those records.

Q. Did Merck or Merck's attorneys provide you with any documentation that showed when they provided the first payments for Dr. Le's study?

ATTORNEY RATLIFF: I object to the form of the question. I don't even know what Dr. Le's study is.

A. So I don't recall seeing any documentation from my attorneys or from Merck about their funding or provision of drug for the MSI study.

Q. All right.

ATTORNEY BROWN-MARSHALL: I'd like to mark as Exhibit 2131.

- - -

(Whereupon, document JHU2131, is received and marked as Exhibit 2131 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2131.

THE WITNESS: Thank you.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, I'll represent to you that this is one of the exhibits Dr. Le relied on in her declaration.

A. Okay.

Q. Okay?

And do you see on the first page where it says: Investigator initiated clinical trial research agreement?

Do you see that?

A. Yes, I see that.

Q. Okay. Did you review this document in preparing your declaration?

A. I don't recall.

Q. Okay. And if you would just flip to the back page, last page of the exhibit. Do you see that there are some signatures?

A. Yes.

Q. And you see at the bottom it's signed by Dr. Dung Le, M.D., principal investigator?

A. Yes.

Q. Do you see that? Okay.

And then the line above, it's also

signed by a representative of the Johns Hopkins University, the associate dean of research administration.

Do you see that?

A. Yes.

Q. And then it's also signed by Eric H. Rubin, M.D., on behalf of Merck Sharp & Dohme.

Do you see that?

A. Yes.

Q. And you did not review this exhibit in preparing your declaration?

A. I do not recall.

Q. All right.

ATTORNEY BROWN-MARSHALL: I'd like to mark as Exhibit 2408.

- - -

(Whereupon, document entitled Amendment #1, is received and marked as Exhibit 2408 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2408.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, are you

familiar with this document?

ATTORNEY RATLIFF: And I object to Exhibit 2048 --

THE WITNESS: 2408.

ATTORNEY RATLIFF: Thank you.

I object to Exhibit 2408 for purposes of authentication, foundation, and hearsay.

A. I do not recall looking at this document.

BY ATTORNEY BROWN-MARSHALL:

Q. Okay. So you didn't review this document in preparing your -- strike that.

You did not review Exhibit 2408 in formulating your opinions in your declaration; correct?

A. I do not recall doing that.

[redacted]

A. I see that, yes.

ATTORNEY BROWN-MARSHALL: I'd like to mark as Exhibit 2409.

- - -

(Whereupon, document entitled

Amendment #2, is received and marked as Exhibit 2409 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2409.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, are you familiar with Exhibit 2409?

ATTORNEY RATLIFF: I object to Exhibit 2409 for the purposes of authentication, foundation, and hearsay.

A. So can I just ask was this included in Dr. Le's declaration?

Q. No, it was not.

A. So I'm not familiar with it.

[redacted]

A. I do not believe so.

Q. And Merck's attorneys did not provide this document to you?

A. I do not recall ever seeing it before.

ATTORNEY BROWN-MARSHALL: I'd like to mark as Exhibit 2410.

- - -

(Whereupon, document entitled Amendment #3, is received and marked as Exhibit 2410 for Identification.)

- - -

CERTIFIED STENOGRAPHER: Number 2410.

BY ATTORNEY BROWN-MARSHALL:

Q. And, Dr. Oberstein, are you familiar with Exhibit 2410?

ATTORNEY RATLIFF: And I'll object to Exhibit 2410 for the purposes of authentication, foundation, and hearsay, and, counsel, do you have another copy of 2410?

ATTORNEY BROWN-MARSHALL: Oh, apologies.

A. I am not familiar with this document.

[redacted]

A. Correct.

[redacted]

[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.

Q. You can put that aside, Dr. Oberstein.

Dr. Oberstein, if you would turn to Paragraph 182 of your declaration. And in the second sentence you write: Dr. Lonberg points to the earlier study of BMS's anti-PD-1 drug that led to a complete response in an MSI-high colorectal cancer patient and reported in Lipson in January 2013 as a comparison to assert that the results the MSI-high study were unexpected because the BMS study failed to produce a response in 32 of 33 patients with colorectal cancer; is that correct?

A. That is what it says.

Q. Okay.

A. I disagree with that statement, but that's what it says.

Q. Okay. So in the BMS clinical trial with this drug nivolumab, they reported one complete response in an MSI-high colorectal cancer patient; correct?

A. That is correct.

Q. And they also reported that it failed to produce a response in 32 of 33

patients with colorectal cancer; correct?

A. Correct. 33 patients were treated. Only one responded and that one had MSI-high colorectal cancer.

Q. Okay. What was the MSI status of the other 32 patients who didn't respond?

A. I don't believe that was reported by BMS.

Q. Okay. So that was not known at the time?

A. I don't believe it was known at the time.

Q. Okay. All right.

If you would turn to Paragraph 185 of your declaration.

A. I'm there.

Q. Okay. And in this paragraph, you are providing opinions on Dr. Goldberg's evidence of a long-felt, unmet need; correct?

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

A. His alleged evidence as I outline, yes.

Q. What is a long-felt, unmet need?

A. A long-felt, unmet need is a sense among the person of ordinary skill in the art and relevant stakeholders that there is no effective or not adequate effective treatments for a certain condition.

Q. And you write that: Dr. Goldberg discusses chemotherapy and targeted therapies available in 2010 to 2015, but does not tie any of this evidence to any of the patent claims; correct?

A. That is correct.

Q. Why would evidence of chemotherapy and targeted therapies available in 2010 to 2015 need to be tied to any of the patent claims?

A. So Dr. Goldberg is proposing secondary considerations and proposes that they justify or help speak to the nonobviousness of the patent claims. He doesn't discuss or connect them to any of the patent claims.

Q. Well, chemotherapy and targeted therapy as available in 2010 to 2015, those are therapies that are described in the prior

art; correct?

A. That is correct.

Q. Okay. Why would you need to tie the prior art to the patent claims in order to demonstrate a long-felt, unmet need?

A. So the long-felt, unmet need for certain treatment should be relevant to the treatment that you are going to propose to fill that unmet need.

And I think that the person of ordinary skill in the art who would have access to MSI-high study record and prior art references that suggest that immunotherapy will be effective in MSI-high colon cancer would anticipate that pembrolizumab or PD-1 antibodies would be effective and would be worth conducting a trial to test in MSI-high colorectal cancer with an expectation of success. Chemotherapy and other therapies are not relevant to that specific type of therapy.

Q. So as of July 10, 2015, what therapies were available for treating colorectal cancer?

A. So Dr. Goldberg goes through a lot

of those, but they were essentially chemotherapies and several targeted therapies, as well as some other therapies that fall into the greater rubric of targeted therapy, but a person of ordinary skill in the art as of July 10, 2015 would have been aware of the MSI-high study record, the previous art references, and would have been motivated to treat an MSI-high colorectal cancer patient with pembrolizumab with a reasonable expectation of success.

Q. So as of July 10, 2015, Keytruda had not received FDA approval for treatment of any MSI-high cancers; correct?

A. That is correct.

Q. And as of July 10, 2015, Merck had made zero net sales of Keytruda for colorectal cancer patients; correct?

A. So I don't know that, but I -- I don't know that.

Q. Okay. Did you speak with Dr. Sheridan about his analysis of the sales of Keytruda for colorectal cancer?

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

trials; correct?

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

A. So a clinical trial is not available outside of a clinical trial. There are therapies, of course, that are available off-label as you say.

Q. And any prescription of either Keytruda or nivolumab outside of the clinical trial as of July 10, 2015 would have to be off-label; correct?

ATTORNEY RATLIFF: For any use? I object to the form of the question.

A. So there were FDA approved indications of pembrolizumab as of July 10, 2015.

Q. So any prescription of either Keytruda or nivolumab for a patient with MSI-high colorectal cancer outside of a clinical trial as of July 10, 2015 would have to be off-label; correct?

A. That is correct.

Q. Dr. Oberstein, did you review any statements by Merck to the FDA regarding

metastatic MSI-high colorectal cancer patients representing a group of patients with a high unmet medical need?

A. I don't recall.

ATTORNEY BROWN-MARSHALL: If you want, we can take a short break, and I can figure out if I have any additional questions?

ATTORNEY RATLIFF: Sure.

CERTIFIED STENOGRAPHER: Off the stenographic record at 3:09 p.m.

- - -

(Whereupon, a short recess was taken.)

- - -

CERTIFIED STENOGRAPHER: Back on the stenographic record at 3:20 p.m.

BY ATTORNEY BROWN-MARSHALL:

Q. Dr. Oberstein, is it your opinion that as of July 10, 2015, metastatic MSI-high colorectal cancer patients did not represent a group of patients with a high unmet medical need?

A. So that is not my opinion. I think that MSI -- I'm sorry, MSI-high colorectal

cancer?

Q. Yes.

A. So I think that as of July 10, 2015, MSI-high colorectal cancer patients did qualify as a high unmet need. That was the question?

Q. Yes.

ATTORNEY BROWN-MARSHALL: I have no further questions.

Thank you for your time today.

THE WITNESS: Okay.

ATTORNEY RATLIFF: So, Doctor, I do not have any questions for you.

However, I request that this transcript be designated highly confidential under the protective order, and, counsel, we can work out what portions should be not under the confidentiality of the protective order.

We're done.

(Continued on next page for jurat.)

CERTIFIED STENOGRAPHER: Off the stenographic record at 3:21 p.m.

- - -

(Time noted: 3:21 p.m.)

- - -

_____
PAUL E. OBERSTEIN, M.D.

Subscribed and sworn to before me this _____ day of _____ 2025.

_____
Notary Public
My Commission Expires:

/

/

I wish to make the following changes, for the following reasons:

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C E R T I F I C A T E

I, RICHARD GERMOSEN, Fellow of the Academy of Professional Reporters, stenographic New Jersey Certified Court Reporter, New Jersey Certified Realtime Court Reporter, California Certified Shorthand Reporter, California Certified Realtime Reporter, NCRA Registered Diplomate Reporter, and NCRA Certified Realtime Reporter, do hereby certify:

That PAUL E. OBERSTEIN, M.D., the witness whose deposition is hereinbefore set forth, having been duly sworn, and that such deposition is a true record of the testimony of said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 20th day of February 2025.



_____

RICHARD GERMOSEN,
FAPR, RDR, CRR, CCR-NJ, CRCR, CSR-CA, CCRR-CA,
NYACR, NYRCR
LICENSE NO. 30XI00184700
LICENSE NO. 30XR00016800
California CSR No. 14391
California CRR No. 198

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