UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME LLC,

Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,

Patent Owner.

_____

IPR2024-00240

Patent No. 11,591,393

_____

DEPOSITION OF RICHARD M. GOLDBERG, M.D.

Conducted Virtually

Friday, December 13, 2024

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Reported by: Monique Vouthouris, CCR, RPR, CRR

DEPOSITION OF RICHARD M. GOLDBERG, M.D.

pursuant to notice, conducted virtually via Zoom Videoconference, before Monique Vouthouris, Certified Court Reporter, Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the States of New Jersey and New York.

A P P E A R A N C E S

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KELLI WELCH, Planet Depos Technician

C O N T E N T S

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E X H I B I T S

(Exhibits attached to transcript.)

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Exhibit 1115 Recent Therapeutic Advances in the Treatment of Colorectal Cancer by Ciombor, et als. 98
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P R O C E E D I N G S

RICHARD M. GOLDBERG, M.D.,
being first duly sworn or affirmed by the Notary, testifies as follows:

EXAMINATION

BY MR. ZEILBERGER:

Q Good morning, Dr. Goldberg.

A Good morning.

Q My name is Daniel Zeilberger with the Paul Hastings law firm. I'm appearing today for petitioner Merck. I'm joined today by Preston Ratliff, Isabella Cazacu, and Jinny Lim, also with Paul Hastings and appearing for petitioner Merck.

In addition, Merck in-house counsel Karen Moreira is also on the line, and Mark Stewart may also join at some point today.

How are you feeling today, Dr. Goldberg?

A I'm feeling good.

Q Do you understand that you're testifying under oath today?

A I do.

Q Is there any reason you cannot testify truthfully today?
A No.
Q You retired from medical practice in 2019, correct?
A That's correct.
Q And you stopped seeing patients earlier in 2017, correct?
A I saw a few patients when I was at WVU, mainly covering the inpatient consult service, but I didn't see patients in clinic.
Q In this matter you're being compensated $900 per hour, as well as an additional $450 per hour for travel, correct?
A That's correct.
Q Is that your standard hourly rate?
A It is for legal cases.
Q Do you have a different hourly rate for non-legal cases?
A I do consult with companies, big pharma and small start-ups, as well as technology companies, and I adjust my rates downward for companies that are

less well-capitalized.

Q For those activities what is your hourly rate?

A So for big pharma it's 6 to $700 an hour. For smaller start-up companies it's $500 an hour.

Q And which companies do you consult for?

A It's about a dozen. I can look up the list, if you would like a comprehensive list, but I'll have to find it on my computer.

Q Sitting here today, which companies can you recall consulting for?

A Taiho, Takeda, AstraZeneca, Agenus, Valor Pharmaceuticals, Compass Technologies, Focal Medical. Let's see. Modulation Therapeutics.

I'm going to just open my email because I have files on the email for each of the companies that I work with that will help to remind me if there's anybody else that I've left off.

AbbVie, Artemida, Inspirna, International Cellular Therapeutics, GlaxoSmithKline, GeneCentric.

I think that's a full list, but there may be several missing. That's what I can recall.

Q Okay. And all of that consulting work has been done after you retired?

A I did do some consulting before I retired, but this is a recent list within the last two years.

Q Approximately how much time have you spent working on the matter for which you are here today?

A I'm just going to generally recall, I would guess it's more than 30 hours, but I can't be precise.

Q Who first contacted you about this case?

A I was first contacted by Dung Le, who is a physician at Johns Hopkins University that I've collaborated with over the years, to ask if I had an interest in potentially representing Johns Hopkins in this matter.

Q And what did Mr. Dung Le tell you about this case?

A So Dung Le is a woman. She told me that Merck had patented -- or that Johns Hopkins University had patented some indications related to the use of pembrolizumab in microsatellite instability and had a dispute with Merck about the

validity of that patent and required someone such as me who had experience with pembrolizumab, participated in the initial clinical trial KEYNOTE-017. And I was knowledgeable about the management of gastrointestinal cancer patients, in particular colorectal cancer patients, both before, during and after the initial studies with pembrolizumab in that setting.

Q Did Dung Le tell you what you would be testifying about in this proceeding?

A No. She just asked me if I was interested, and then said she would have somebody from the Fish law firm contact me to give me further details.

Q And so did you tell Dung Le that you were interested in working on this case?

A I told her I was interested in speaking with the legal team to find out more details about what the case entailed.

Q So after speaking with Dung Le, was the next person you spoke to an attorney from Fish & Richardson?

A I believe it was, yes.

Q When were you retained for this case?
A It was sometime early this year. I don't recall exactly when. I could check my records if it's important.
Q Do you recall when you started working on this case?
A Give me a minute and I'll look in my email files so that I can be more precise.
So the first record I have of a contact with a Fish lawyer is with Todd Miller and it occurred on February 8th, 2024.
Q And what did Todd Miller tell you about this case?
MS. BROWN-MARSHALL: Objection, counsel. I'm going to object to the extent that this calls for attorney-client privileged information.
And I would caution the witness not to disclose any conversations with counsel, the content of any conversations with counsel.
Q Dr. Goldberg, were you already retained by JHU on February 8th, 2024?
A Let me just look and see.

So I have a letter dated February 13th, 2024 from Christina Brown-Marshall, who is on this call, stating, "In follow-up of our recent conversations, this letter confirms that you have agreed to act as an independent consultant assisting Fish & Richardson, counsel for Johns Hopkins University, in connection with the litigation styled Merck Sharp & Dohme LLC versus John Hopkins University, Case 1:22-cv-03059-JRR. This letter contains the terms of our agreement."

Q So on February 8th, 2024 in the communication you received from Todd Miller, what did you -- what information did you receive?

A Well, that's a long time ago, but my memory is that he gave me a thumbnail sketch of the issues in the lawsuit, and asked me about my experience relevant to the development of pembrolizumab for the indication of treatment of MSI-high cancers and MSI-high colorectal cancers in particular. And we agreed that I had the relevant experience that he felt was needed to represent the interests of Johns Hopkins University in this case.

Q And so what you just communicated to me, that was all contained in this email you referred to from February 8th?

A No. We had a telephone discussion about this, and as a consequence of that telephone discussion, a letter was generated by Ms. Brown-Marshall that detailed the agreement that we were going to work under.

Q So what was said to you in the February 8th email that you referred to?

A Let me go back to that email.

So we decided to -- that we could work together. I did disclose to Mr. Miller that I was consulting with Merck as a member of the data safety monitoring boards of several phase III studies that were being conducted by Merck, and that that would represent a potential conflict of interest for me, and that I was prepared to resign from those data safety monitoring boards, which I subsequently did.

Q So what did you see your assignment in this case as?

A I believe that my assignment was to

particularly provide the background and testimony related to the fact that the use of pembrolizumab met an unmet need in the management of patients with colorectal cancer in particular.

I've also been asked to prepare some information regarding the non-colorectal indications for pembrolizumab that, as I understand it, that is not relevant to today's discussion.

Q Before working on the present matter, have you ever worked with the Fish & Richardson law firm?

A I have not.

Q Okay. I know you have a computer in front of you today. Do you have anything else with you today?

A I do. I have a copy of my declaration that's clean, I have a bottle of water, and some Kleenex.

Q And on your computer, just so I understand what sort of setup you have, what do you have on your screen?

A I have this Zoom call and a toolbar.

Q Do you have any of the files or exhibits

relating to this proceeding on your computer?

A They're on my computer, but they're not open or on my screen.

Q And you said you have a clean copy of your declaration printed out. Do you have any of the exhibits that are cited in your declaration in hard copy form?

A I don't have them, but I believe that Casey has some of them. They're not visible to me.

Q Okay. And who is in the room with you today?

A Casey.

Q Anyone else?

A Just the two of us.

Q And I know you said your declaration is a clean copy, but are there any Post-it notes or tabs or anything like that on your declaration?

A No.

Q How much time did you spend preparing for today's deposition?

A Well, I would consider all the time that I've spent working with Fish to be in preparation for

today's deposition. So I'm going to guess that over time it was more than 30 hours prior to this week and then probably another 15 hours this week.

Q And was that most recent 15-hour preparation time by yourself or with other people?

A Most of it was by myself, but some of it was with Casey or with Chrissy.

Q Other than Casey and Chrissy, did you speak with anyone else in the most recent time, the 15 hours of preparation for your deposition?

A I did not.

Q The declaration that you have in front of you today, on the cover page is it marked JHU 2090 on the bottom right?

A It is.

Q And the cover page is signed on October 4th, 2024, correct?

A By me, yes.

Q And that's your signature on the cover page?

A It is.

Q Did you read your declaration carefully

before you signed it?

A Well, I wrote the declaration, and, yes, I did read it carefully before I signed it and I've read it many times since.

Q Okay. And you say you wrote your declaration. You wrote it by yourself?

A I wrote the initial draft by myself. Then I sent it off to the Fish attorneys, who read it over, and we revised some of the language in the report based on our conversations.

Q Were there any substantive changes between this initial draft you wrote by yourself and the version that was eventually signed on October 4th, 2024?

A So some of the language in this is legal language that, generally, when I am quoting that language, I say I understand from my discussions with the lawyers that. And so I'm not a lawyer, I'm a physician and researcher, and so I required some teaching from the lawyers about what was proper to put in the deposition regarding the legal tenets of the dispute.

Q Did you make any changes relating to the science that you discuss in your declaration between the initial draft and the version that was signed on October 4th, 2024?

MS. BROWN-MARSHALL: Objection; vague.

A So I don't remember specific changes, but, you know, it was a work in progress, and each time I read it I made some changes. So it was a work in evolution before it was finalized and signed.

Q For the eventual version of your declaration that was signed, did you understand every statement, opinion, and conclusion that's contained in your declaration?

A I believe so. You know, some of the legal language is a bit arcane, and sometimes I need to be reminded of the specific meanings of some of the legal phrases. And if that is relevant today, I'll tell you what the issues are.

Q But sitting here today, are you aware of any statements, opinions, or conclusions contained in your declaration that you do not understand?

A I believe I understand it.

Q And you are familiar with the content of the documents that you reference in your declaration. Is that right?

A Yes.

Q Are there any errors in your signed declaration?

A There are a few places where I noticed there was a missing word, something like a "which" or a "to" or an "a," but that didn't change the meaning of the sentences.

Q Do you have any corrections to your signed declaration that you wish to make today?

A I didn't catalog the places where there was a missing word. I can, if that's necessary, and supply that information to you, or we can point it out as we go through the report. None of it changes the meaning of the sentences.

Q The declaration you have in front of you relates to U.S. Patent No. 11,591,393, correct?

A Correct. I believe it's referenced as the '393 patent throughout my report.

Q Okay. And if I refer to it today at any

point as the '393 patent, you'll understand what I'm talking about?

A I will.

Q Did you review the '393 patent?

A I have.

Q Do you understand the '393 patent?

A I believe so.

Q What experience do you have that enables you to understand the '393 patent?

MS. BROWN-MARSHALL: Objection; vague.

A So, you know, I could start with my experience as a GI medical oncologist, my experience as an expert witness in other cases. I'm not sure exactly what you're asking me. Do you want a two-minute response or a 20-minute response?

Q I just want to understand what experience you think makes you qualified to understand and opine on the '393 patent.

A So have you read my report?

Q I have.

A Okay. So the first -- first 15 pages discuss my qualifications as a GI medical oncologist,

a clinical trialist, a medical researcher, a medical teacher, an author of multiple publications, an editor for multiple medical journals, and my experience caring for thousands of patients, including thousands of patients with colorectal cancer.

So I believe -- and I would also add my interest in and experience working with genetic predisposing syndrome, such as Lynch syndrome, related to colorectal cancer.

I also have served as an expert witness in two other patent disputes. One was a patent dispute where I represented Genentech against Amgen, who had a generic version of bevacizumab known as MVASI, and that case was settled after deposition, but outside of court.

And then I represented Taiho in a dispute with five generic drug companies that I believed that the patent that they had for LONSURF, which is a combination drug used to treat colorectal cancer, was obvious and invalid, and Judge Connolly in Delaware ruled in favor of Taiho in that dispute.

So those are my two patent law testimony experiences.

I've also been a witness in several malpractice suits where I've represented the physician, but none of those are recent.

Q In preparing your declaration, did you have any conversations with any JHU employees or scientists?

A I did.

Q Who?

A So I had conversations with Dung Le, who is the first author of the New England Journal of Medicine paper on the KEYNOTE study and who I worked with closely as we were enrolling patients in that study.

I also had some conversations with Luis Diaz, who is also a member of the Hopkins team, who was the individual who first had the insight that the one of 33 patients who responded to nivolumab in the Topalian study might have microsatellite instability.

I also spoke with several of the other expert witnesses retained by Johns Hopkins in

preparation of their reports.

Q What did you speak to Dung Le about in your conversations with her?

A Well, the main purpose of my conversation with her was to get an update on the study. There have been two manuscript publications, one in the New England Journal of Medicine and another in Science, both of which were interim reports. I was interested to know what the five-year survival data was for patients who had been enrolled in the study, and that is not information that is in the public domain, although, as I understand it, that information has been submitted for consideration for an upcoming ASCO meeting. It is not yet published.

Q Why were you interested in knowing the five-year survival data?

A Because so many -- so I ended up treating, I believe, four patients on the study. Two of them had very advanced disease. Both of them are disease-free. It's now close to 10 years from the time that they initiated treatment. And that suggested to me that there was a high rate of

long-term survival among these patients. And so it was of great interest to me, as it is to the medical community, to know what the median overall survival was for the three categories of patients treated on the three-arm study.

Q Do you discuss the five-year survival data in your declaration?

A I do.

Q And you said that the main purpose of your conversation with Dung Le was what you just said. Is there anything else you discussed with Dung Le?

A I don't remember all of the details, but that was the main point of the discussion. I did also read her -- her declaration.

Q Do you remember any of the other details?

A I think we exchanged some pleasantries and we talked about plans to present at future scientific meetings.

Q Why did you speak with Luis Diaz?

A Well, Luis Diaz and I have been friends and coworkers for many years and we see each other frequently at meetings.

You know, this finding was one that in many ways revolutionized our thinking about the treatment of MSI-high cancers and is a great success that we both participated in and so it's a common reason for celebration when we get together.

Q But you said you spoke to Luis Diaz to prepare your declaration. Why did you see fit to do that?

A Maybe I should correct that and say I spoke with Luis Diaz while I was preparing my declaration, but I didn't have a specific question for him and he didn't provide me with any additional information that wasn't already known to me.

Q Did you reach out to him?

A Well, we see each other at meetings, you know, we say hi to each other and shake hands and talk about the good times.

Q Got it. So you saw him at a meeting and that led to talking about how you're preparing a declaration in this proceeding?

A Correct.

MS. BROWN-MARSHALL: Objection;

mischaracterizes previous testimony.

Q You said you spoke to other experts. Which other experts?

A So I spoke with Nils -- is it Lundgren? -- who is the former employer of Merck Sharp & Dohme, who is an expert witness on the background of the development of PD-1 inhibitors. And then I also spoke with an economics expert, but I don't remember that person's name.

Q What did you speak about with Nils Lundgren?

A I spoke about his experience with the development of PD-1 inhibitors while he was employed at Merck and/or -- I'm sorry, at BMS. And we also talked about the mechanism of action of PD-1 inhibitors, their engagement with T cells, and how the biology is understood at this time. And we talked about the novelty of the findings that came out of the treatment of MSI-high patients.

And he is not a clinician, so I provided him with my clinical experience with the drugs. He provided me with his laboratory and scientific

perspectives on the development of PD-1 inhibitors.

Q And just to be clear, I think you said "Nils Lundgren." Do you mean Dr. Nils Lonberg?

A Right. Sorry, I couldn't remember the details of his last name.

Q Did you rely on the information that Dr. Lonberg provided to you in preparing your declaration?

A I don't remember the exact timing of my discussion with him, but my memory is that our discussion occurred after I had signed my report.

Q What about your discussion with the economic expert that you referred to, was that before or after you prepared your report?

A Again, it was around the same time, and I believe it was after I had prepared my report. I don't make any reference to the economic issues in my report.

Q Why did you speak to the economic expert?

A Well, I had interest in the economics of pembrolizumab and that person was expert in that, and it was one of the indicia that I think supports the

patent in that there was commercial success with the agent and I was interested in learning about that.

Q You don't discuss any commercial or alleged commercial success in your declaration, though, correct?

A I don't believe so. If I do, it's just in passing. It wasn't the point of my testimony.

Q Did you provide any opinions or information to either Dr. Lonberg or this economic expert that you're referring to?

A I don't believe that I did.

Q Other than the people you've already identified and any attorneys at the Fish & Richardson law firm, did you speak with anybody else as part of this proceeding?

A I did not.

Q If you could please open your declaration to paragraph 55.

A Okay. I've opened it. Do you want me to read the paragraph or are you going to point out --

Q No. So in the first sentence of paragraph 55 you say that you understand from conversations

with the JHU scientists that when they tried to interest the research teams at either BMS or Merck in funding the trial to test their hypothesis, neither companies' teams were interested, correct?

A I see that statement.

Q When you referred to JHU scientists in paragraph 55, who were you referring to?

A I'm referring to Dr. Le and to Dr. Diaz.

Q So this is information that both Dr. Le and Dr. Diaz informed you of?

A Well, I also have some other sources for the statement, which I can tell you about, if you would like.

Q Well, in your declaration you don't cite any other sources, correct?

A Not here, that's correct. I do cite the cancer letter at the bottom of the page 35 is the reference there, and the sentence that the 35 indicates is, I'll read it to you, "because they were unable to obtain pharmaceutical company funding, they funded it with JHU resources and obtained additional support through a grant from the charitable

organization Swim Across America."

If you read the New England Journal of Medicine paper, it cites several other charities that provided some resources for the study. But I believe the largest amount of support came from Swim Across America.

Q And when you say that the JHU scientists tried to interest the research teams at BMS and Merck, what did the JHU scientists do to try to interest those research teams?

A You would have to ask them that question.

Q You don't know what they did to try to interest the research teams at BMS and Merck, correct?

A I can speculate on it if you would like me to, but they didn't specifically tell me what their arguments were.

Q Shifting gears, you have been affiliated with groups that develop, run and analyze trials to advance cancer treatment and the understanding of cancer biology, correct?

A Correct.

MS. BROWN-MARSHALL: Objection; vague.

A So I've worked with National Cancer Institute funded cooperative groups, oncology cooperative groups that sponsor clinical research and translational research in cancer patients.

My specific area of interest is gastrointestinal cancer, subset specific area of interest is colorectal cancer.

I've also been involved in the administration of those groups. I've run the GI committee for a now defunct group called the North Central Cancer Treatment Group. That group merged into what is now called The Alliance.

I also worked prior to the merger with the Cancer and Acute Leukemia Group B, known as CALGB, and I chaired the GI committee for that.

Once The Alliance was formed from the merger of those two groups plus The American College of Surgeons Oncology Group, I became the associate group chair for The Alliance where my responsibilities went beyond just GI cancer to the administration of the entire group. I also serve on

the board of directors of that group and on the board of directors of the Alliance Foundation.

Q How many trials have you personally developed to advance cancer treatment and the understanding of cancer biology?

MS. BROWN-MARSHALL: Objection; vague, compound.

A So I can't give you a precise number. But I can tell you that personally I've been the principal investigator on dozens of trials.

In my role as the GI committee chairs for NCCTG and CALGB, I administered a portfolio of studies and was responsible for the development of probably over a hundred protocols, but that's just a guess. I then investigated issues in GI cancers that include anywhere in the GI tract from the esophagus to the anus.

I also participated in early phase studies in that we had a phase 1 program when I worked at Mayo Clinic, when I worked at University of North Carolina, and when I worked at Ohio State where we were doing first-in-man studies of new agents or

first-in-man studies of combinations of agents that had been previously approved but not tested together.

So I have a long experience in clinical trials that ran just from phase 1 two to three clinical trials and I describe those trials in my declaration.

Q So it's fair to say, Dr. Goldberg, that over the course of your career, you've been involved in and analyzed many cancer-related clinical trials?

A I have. You know, I have over 400 peer-reviewed publications. I also work with international groups that do Gould analyses of clinical trials from across the world, and I have publications with many of the leading clinical trialists in GI oncology.

Q In addition to drafting your own publications relating to clinical trials, I assume you also have reviewed many publications relating to clinical trials over your career. Is that fair?

A Well, I've reviewed every one of the 400 publications that I'm a co-author on. I also have been a reviewer for many prestigious medical

journals, including the New England Journal of Medicine, The Lancet, the Annals of Oncology, the Journal of Clinical Oncology, JAMA, JAMA Oncology.

In addition, I serve as the executive editor and previously the GI oncology editor for the online medical textbook known as UpToDate where we evaluate the outcomes of studies and relate them to the entire body of knowledge that clinicians would use to manage patients. And this UpToDate textbook is the go-to reference for I would say the majority of physicians in the U.S. and is available internationally as well.

Q You believe you played a role in getting pembrolizumab approved for its MSI-high colorectal cancer indication, correct?

MS. BROWN-MARSHALL: Objection; vague.

A Yes.

Q I couldn't hear you over the objection, Dr. Goldberg. Can you please repeat your answer?

A Yes, I think I played multiple roles.

MR. ZEILBERGER: And I'll just note, counsel, you've done it many times now, making

speaking objections that are improper at the PTAB. I'll ask you to refrain from doing so over the course of the remainder of the deposition.

MS. BROWN-MARSHALL: Counsel, I made a short two-word objection.

MR. ZEILBERGER: You made an objection that is specifically listed as an improper objection in the Patent Trial Practice Guide.

MS. BROWN-MARSHALL: Counsel, we'll continue.

MR. ZEILBERGER: Are you confirming that you'll refrain from improper objections, counsel?

MS. BROWN-MARSHALL: No. I said, counsel, we'll continue the deposition.

MR. ZEILBERGER: Okay. I am noting for the record that the Patent Trial Practice Guide at page 128 specifically says examples of objections that would not be proper are "objection; vague."

BY MR. ZEILBERGER:

Q Dr. Goldberg, if you could please turn to paragraph 66 of your declaration.

A I have that in front of me.

Q In paragraph 66 you indicate that you prescribed pembrolizumab to your MSI-high colorectal cancer patients until you stopped seeing patients in 2017, correct?

A Right.

Q So you prescribed pembrolizumab for two years, correct?

A Well, I prescribed pembrolizumab as part of the clinical trial starting in 2013, so my experience with it really is at least four years.

Q Outside of the context of the clinical trial, you prescribed pembrolizumab for two years, correct?

A Well, the FDA approval I believe was in 2017, and so I only had an opportunity to prescribe it after it was FDA approved.

Q Pembrolizumab is a PD-1 inhibitor, correct?

A Correct.

Q Is pembrolizumab the only PD-1 inhibitor that you prescribed to MSI-high colorectal cancer patients?

A Yes.

Q Are you aware that there are other PD-1 inhibitors that are approved for MSI-high colorectal cancer?

A I'm aware that there are other PD-1 inhibitors that are approved for MSI colorectal cancer, but they were not approved prior to 2017 when I ceased practicing.

Q Got it. So those other PD-1 inhibitors were not options during the time period when you were prescribing PD-1 inhibitors?

A Well, nivolumab was on the market, but it did not have this indication, so I wouldn't have prescribed it.

Q Moving forward to paragraph 72 of your declaration.

A I have it in front of me.

Q Thank you. You indicate in paragraph 72 that at Ohio State University you rapidly adopted universal MSI testing for your patients and used PD-1 inhibitors when appropriate, correct?

A I see that.

Q Which PD-1 inhibitors are you referring to

in paragraph 72?

A Well, I left Ohio State at the end of 2017. I was using pembrolizumab in the GI oncology clinic, as were the other GI medical oncologists that I worked with.

Ohio State University has a full service cancer hospital and so we were also treating patients with lung cancer and melanoma and bladder cancer. I was the physician in chief of the cancer hospital. So individuals who reported to me were using nivolumab for the approved indications in their disease sites. But in the GI oncology group we were exclusively using pembrolizumab, to my knowledge, at that time.

Q And when you say "when appropriate" in paragraph 72, what are you referring to?

A According to the FDA-approved indications, or if a patient was eligible for a clinical trial that included a PD-1 inhibitor, it would be appropriate to administer it as part of the clinical trial.

Q Are there any instances when a patient

would fall under the FDA-approved indications but it would not be appropriate to give them a PD-1 inhibitor?

MS. BROWN-MARSHALL: Objection to the form of the question.

A So if you read the package insert for PD-1 inhibitors, including for pembrolizumab, it does have a number of cautions such as the use of PD-1 inhibitors in individuals with autoimmune disease, which can be exacerbated by administration of PD-1 inhibitors.

So the short answer to your question is yes, there are contraindications to the use of PD-1 inhibitors.

Q You alluded to it earlier today, you are familiar with the clinical trial study of pembrolizumab in patients with microsatellite unstable tumors that first publish as a study record on June 10th, 2013, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So can you tell me which KEYNOTE study that

is?

Q Sure. I can direct you to page 11 of your declaration, footnote 2.

A Restate your question.

Q You are familiar with the study of pembrolizumab in patients with microsatellite unstable tumors that first published as a study record on June 10th, 2013, correct?

A Correct.

MS. BROWN-MARSHALL: Object to the form of the question.

Q If I refer to this study as the 2013 MSI-high study, will you understand what I'm referring to?

A Yes.

Q You participated in the 2013 MSI-high study, correct?

MS. BROWN-MARSHALL: Objection; form.

A I enrolled patients on this study and I was the principal investigator at Ohio State for this study.

Q How did you first learn of the 2013

MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I learned about the study when Bert Vogelstein, who worked at Johns Hopkins University and led the lab that has made the seminal discoveries about the biology of colorectal cancer, contacted my friend and colleague Dr. Albert de la Chapelle. Dr. de la Chapelle was a molecular geneticist who worked at Ohio State University and helped to elucidate the mechanism behind microsatellite instability, both as it applies to patients with Lynch syndrome, who inherit it, and as it applies to patients who have hypermethylation of their DNA and therefore have microsatellite instability that's acquired and not inherited.

Dr. Vogelstein and Dr. de la Chapelle were close colleagues, and Dr. Vogelstein contacted Albert to see if there might be an interest in participating in this clinical trial from the GI team at Ohio State.

Q What made Ohio State want to participate in

the 2013 MSI-high study?

MS. BROWN-MARSHALL: Objection to the form of the question.

A So I would say that there were multiple reasons. One was the long-standing collaboration between Dr. Vogelstein and Dr. de la Chapelle.

Two was we had a very strong clinical genetics program at Ohio State and had multiple publications in prestigious journals, like the New England Journal of Medicine, about screening patients for Lynch syndrome, and so we had expertise in the molecular genetics that would be required to be a full participant in the study.

We also -- the James Cancer Hospital, of which I was physician in chief, is the third largest cancer hospital in the country. So not only does it have a large volume of patients with inherited cancer predisposition syndromes, such as Lynch syndrome, it has a large volume of patients in general, and there's always a desire for clinical trials such as this to come to a rapid answer.

I believe that from the Hopkins

perspective, they wanted to harness the engine that we could provide for patient accrual. We, of course, were very interested in working with Dr. Vogelstein, he's one of the most impactful and highly published researchers in medicine and has made seminal discovery in the molecular underpinnings of colorectal cancer, and I think any oncologist and researcher would consider it a privilege to work with his team.

So there were many reasons for us to want to participate in the study.

Q As part of your answer you said there was a desire to come to a rapid answer. What do you mean by that?

A Well, when a hypothesis is generated, there's an interest in finding out if the hypothesis is true or not. And there are many trials that are created that never fully accrue and, therefore, are unable to answer the question that they were designed to interrogate.

And so it's common for large cancer centers, such as Ohio State and Johns Hopkins and

others, to enter into consortia agreements so that their accrual engines can be harnessed to answer questions as rapidly as possible.

Q For this particular study, why was there a desire to come to a rapid answer?

MS. BROWN-MARSHALL: Objection to the form of the question.

A So I don't think it was peculiar to this study. I think we want to answer questions quickly so that we can garner the value of the question that we answered and either move it forward or discard it if it turns out that the hypothesis was not confirmed.

You know, we feel great pressure to cure cancer patients. And until we can cure every cancer patient, there are unmet needs that researchers, such as myself, feel pressured to try and resolve. So we were trying to do the best we could to both understand the disease and to bring our understandings to the clinic to help our patients.

Q When you were working at Ohio State, was Ohio State proposed with a small number of clinical

trials or a large number?

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, I can't tell you exactly how many clinical trials we had. But, you know, we had a 3,000-bed -- or 300-bed cancer hospital that was full every day. We had hundreds of physicians seeing cancer patients. We had a very large clinical trials office and participated in many NCI and pharmaceutical sponsored as well as investigator initiated clinical trials. You know, that was our reason for being.

Q Got it. So are you saying that Ohio State was willing to participate in most clinical trials that were proposed to them?

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, we're always interested in having clinical trials to offer to our patients because often they provide either cutting edge new trials that are new -- access to new drugs that patients clamor for, and we wanted to advance cancer

treatment.

You know, if we didn't think a study was a good study, we would evaluate it and not approve it. But we were receptive to opportunities to expand the repertoire of things that were available to our patients when we considered them to be proper and meaningful.

Q Were most clinical trials accepted or rejected at Ohio State?

A Well, I don't have a statistic on that. But I think that we would accept more clinicals trials than we would reject. It would take something specific to reject a trial.

For example, if I had a first line metastatic colorectal cancer trial and somebody approached with me another first line colorectal cancer trial that completely overlapped in terms of eligibility, we would say we already have a study for that, and therefore we're not interested in another study that would compete with the study we've already committed to. Or if we said, okay, well, we don't see this rare type of tumor, and therefore we can't

spend the resources to open the trial and keep it running because we're unlikely to be able to contribute much to the -- to satisfy the accrual goals of this study.

So it's a complicated series of considerations that balances institutional resources with institutional and investigator interests and patient interests.

MS. BROWN-MARSHALL: Counsel, we have been going for over an hour now. Is now a good time to take a break?

Q Dr. Goldberg, would you like a break?

A I would.

MR. ZEILBERGER: Sure, we can take a break.

(Recess 10:10 a.m. - 10:15 a.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, you were not involved when the 2013 MSI-high study was being developed between Merck and JHU in 2012, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A The protocol had been finalized when we

were asked to join.

Q And just to be sure, you, yourself, had no involvement in the 2013 MSI-high study before the protocol was finalized, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A That's correct.

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

MS. BROWN-MARSHALL: Object to the form of the question.

A I was not involved in those discussions. I have knowledge from what I was told by Drs. Le and Diaz. And then I also read I believe it was a Forbes article that described the negotiation between Merck and JHU. So those are my sources of information about this.

Q And when you refer to a Forbes article, are you talking about the Forbes article that you cite in your declaration?

A Yes.
Q And did you assume that that Forbes article was accurate for your declaration?
A I did.
Q Merck provided pembrolizumab throughout the 2013 MSI-high study, correct?
MS. BROWN-MARSHALL: Object to the form of the question.
A They had to because there was no other way to obtain pembrolizumab than to get it through Merck.
Q Do you know what the value of pembrolizumab provided by Merck throughout the 2013 MSI-high study would amount to?
MS. BROWN-MARSHALL: Object to the form of the question.
A I have no idea.
Q So when you prescribed pembrolizumab to your patients, you had no idea what it cost?
MS. BROWN-MARSHALL: Object to the form of the question.
A So I'm an academic medical oncologist, and I had no role in purchasing or charging for the drugs

that I prescribed. I just wrote the order according to the indications.

Q During the course of the 2013 MSI-high study, were there any amendments to the study protocol?

MS. BROWN-MARSHALL: Objection to the form of the question.

A I don't recall, but there almost always are amendments to study protocols.

Q Were you involved in any discussions relating to any amendments to the 2013 MSI-high study protocol?

MS. BROWN-MARSHALL: Objection to the form of the question.

A Not that I recall.

Q You don't have any personal knowledge about who drafted the 2013 MSI-high study protocol, correct?

A That's not true. The Hopkins team drafted it is my understanding.

Q I see. So you were involved when the MSI-high study protocol, the 2013 MSI-high study

protocol was drafted?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I'm not sure I understand your question. Are you asking me if I know who drafted the protocol or if I was involved in drafting the protocol?

Q I'm asking if you personally know from your own knowledge who contributed to the drafting of the 2013 MSI-high study protocol.

MS. BROWN-MARSHALL: Object to the form of the question.

A I believe that's stated in the New England Journal of Medicine publication by Le.

Q So the basis of your understanding is what Dr. Le told you?

MS. BROWN-MARSHALL: Object to the form of the question.

A So it's based on what Dr. Le told me and what Dr. Le and we told the world when we published the paper.

Q Can you clarify what you mean when you say that the basis of your understanding is what "we told

the world when we published the paper"?

MS. BROWN-MARSHALL: Object to the form of the question.

A Do you have a copy of the paper?

Q I'm trying to understand, Dr. Goldberg, what the basis is for your understanding about who contributed to the drafting of the 2013 MSI-high study protocol.

A And I was trying to bring up a copy of the manuscript so that you could read what I read in it.

Q So you relied on what you read in the New England Journal of Medicine article of which you're a co-author. Is that right?

A In part.

Q What else did you rely on?

MS. BROWN-MARSHALL: Object to the form of the question.

A So as I've stated, I had discussions with the Hopkins team about how the protocol came to be, and I also read the Forbes article in preparing this declaration.

Q During your involvement in the 2013

MSI-high study, did you communicate with anyone at Merck regarding the study?

MS. BROWN-MARSHALL: Object to the form of the question.

A I did not.

Q How did you obtain the pembrolizumab used for treatment in the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the procedure for opening a clinical trial at Ohio State and other places is that an investigator is engaged by an external party, whether that's Johns Hopkins University or a pharmaceutical company. We discuss the trial with our study teams. If we decide that we're going to engage in the study, then it's presented to the Clinical Trials Office.

The Clinicals Trial Office then goes through the activation process, which includes submitting the clinical trial to the IRB. Once the study is opened, the clinical trials pharmacy has policies and procedures for obtaining the drug, and that is done under my supervision but without my

direct knowledge for a study in which I'm the principal investigator at our institution.

Q Were you involved in selecting patients for the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A I enrolled patients in the study.

Q How did you determine which patients to enroll?

A By reading the study eligibility criteria and exclusion criteria and determining if the patient was eligible.

Q Did you enroll every patient that was eligible for the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So patients enroll in the study. Doctors don't enroll in studies. So I would present a patient that was eligible for the study with the opportunity to enroll in the study. I would give them an informed consent. I would then ask them to read the informed consent. I would then answer any

questions that they had about the informed consent. And if they were interested and eligible, we would then enroll them in the study.

Q Did you present the 2013 MSI-high study to every patient that was eligible for it?

MS. BROWN-MARSHALL: Object to the form of the question.

A I believe not. It's hard for me to say. You know, I presented it to the eligible patients that I saw in clinic. But there were many other patients seen at Ohio State by other GI oncologists and I don't know what they did.

Q During the course of the 2013 MSI-high study, when you saw a colorectal cancer patient, would you always present the 2013 MSI-high study as an option?

MS. BROWN-MARSHALL: Object to the form of the question.

A So, again, presenting a study to a patient requires a complicated number of assessments; one of them is eligibility, one is suitability. So, for example, if you had a patient who is a homeless drug

addict, but was eligible for the study, because of their psychosocial issues, you likely wouldn't consider them to enroll in the study because they would be unlikely to follow all the rules of the study to have interpretable data at the end of their course of treatment.

So not every patient is suitable for a clinical trial and not every suitable patient for a clinical trial agrees to go on it. If you look at the statistics across the United States, less than 5 percent of cancer patients enroll in clinical trials. So the vast majority of patients are never treated on a clinical study.

Q Did you present the 2013 MSI-high study as an option during the course of that study any time you had a patient that was both eligible and suitable for the study?

MS. BROWN-MARSHALL: Object to the form of the question.

A In general, I would present every patient that was eligible with that option, but I can't be certain that I did that a hundred percent of the

time. Many times patients were referred to me from outside the institution because other physicians knew that we had access to pembrolizumab at a time when access was severely limited. And so I would often get patients, for example, from Mayo Clinic, that patient is described by declaration who is sent for me -- sent to me specifically for enrollment in the study after having been managed at another center.

Q How many patients did you enroll in the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So to the best of my recollection, I had four eligible patients enrolled in the study personally.

Q How many of those four patients were MSI-high?

A All of them.

Q You did not enroll any patients in the 2013 MSI-high study that were MSI-low, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A By the time we activated the study, the accrual goal for MSS patients had already been met. The reason for that is 85 to 90 percent of patients with metastatic colorectal cancer are MSS and only 5 to 15 percent of patients with metastatic colorectal cancer are MSI-high. So it was much easier to enroll patients, essentially 1 out of every 10 would be MSI-high, 9 out of 10 would be MSS.

And so it took a while for us to negotiate with Hopkins to open the trial, in part because the amount of money that they were willing to pay on a per case basis was not sufficient to cover the costs of the trial initially until they found some subsequent additional funding.

Q And is that common for a trial to only select patients for a subset of the cohorts at a particular facility?

MS. BROWN-MARSHALL: Object to the form of the question.

A So there's a type of trial called a basket trial in which a particular treatment is given to a particular population of patients and often it will

have multiple arms. Each of those arms will have an accrual goal. As the accrual goal is met for an arm, enrollment to that arm of the study will be closed, but the remainder of the study arms that still have open spots can continue accruing.

And so the trial that we're referring to had three arms; an arm for microsatellite instability high patients with colorectal cancer, an arm for MSS colorectal cancer patients, and an arm for MSI-high non-colorectal cancer patients, each had separate accrual goals, and one arm could be closed while others remained open if that particular arm was fully accrued.

Q So the 2013 MSI-high study was a basket trial?

(Simultaneous speaking.)

MS. BROWN-MARSHALL: Object to the form of the question.

Dr. Goldberg, let me get my objection on the record, please.

Object to the form of the question.

A So it would meet the definition of a basket

trial in that it had several different cohorts of patients being treated with the same intervention.

Q When did Ohio State get the trial started?

A I'm uncertain --

MS. BROWN-MARSHALL: Object to the form of the question.

A I'm uncertain of that date.

Q You said you had four patients that you personally enrolled. Were they all colorectal cancer patients?

A Yes. That was the main population of patients I saw.

Q You referenced earlier patients that were referred to you by physicians at different hospitals. Is that a separate population of patients or is that part of the four that you're referring to?

MS. BROWN-MARSHALL: Object to the form of the question.

A So as a well-known GI oncologist, I would often have patients referred to me for second opinions or for management of refractory disease that came from across the country, when I was at Mayo

Clinic, from across the world.

I also would see patients from Columbus and the surrounding environment who sought me out as their first or only oncologist and I took primary care of them. Some of my referral patients I would see at intervals, but they would get their treatment at home. They would come to see me when there was a question about whether to continue a treatment or a need to change to a different treatment.

So my practice consisted of some oncology patients for which I was the primary oncologist and some for which I was the consulting oncologist.

Q I'm referring specifically, Dr. Goldberg, to your answer earlier when I asked you whether you presented the 2013 MSI-high study as an option, during the course of that study any time you had a patient that was both eligible and suitable, and in response you pointed out how many times patients were referred to you from outside the institution by other physicians.

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, I can't honestly say that I would have offered the study to every single patient. But it was an interesting study and an unmet need, and so I believe I would offer it to anybody who I thought was eligible. But I'm trying to remember back eight or nine years ago.

Q Why did you think it was an interesting study?

A You know, the information about the one patient of 33 in the Topalian study who responded with colorectal cancer to nivolumab and had a sustained and complete response was highly engaging.

The data that Dr. Vogelstein in his laboratory had put together suggesting that this cohort of patients could have a response to a PD-1 inhibitor made scientific sense. We didn't know whether what made scientific sense as a hypothesis would prove to be real when humans were treated with the agent.

There was a great unmet need for helping patients with MSI-high cancers and also patients with MSS cancers, but this study only applied to a subset

of those patients. And as I mentioned, an opportunity to collaborate with the world-class scientists at Hopkins would be appealing to any cancer researcher.

Q While you were involved in the 2013 MSI-high study, you never had to consider whether to recommend the study to a patient with MSS cancer, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So as I stated, by the time we got the study open, the MSS cohort was fully accrued and we did not have the opportunity to enroll MSS patients in the study.

Q Was the MSI-high -- let me rephrase.

Were the MSI-high cohorts ever closed in the same manner as you described for the MSS cohort?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the study eventually met its accrual goals and the trial was closed.

Q Swim Across America provided funding for

the 2013 MSI-high study, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A According to what I was told by the Hopkins investigators, and what's disclosed in the New England Journal of Medicine article, that's true.

Q Do you know whether Swim Across America funds every cancer trial that it's presented with?

MS. BROWN-MARSHALL: Object to the form of the question.

A I have no knowledge of how Swim Across America decides whether or not to fund studies.

Q MSI-high cancer is a relatively rare form of cancer, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So colon cancer is a heterogeneous disease. There are different driver mutations that occur, and in some cases we don't know what the driver mutation is that occurs.

One subset of colorectal cancer is driven by a defect in mismatch repair. That is indicated by

microsatellite instability. It's estimated that in advanced cancer, 5 to 15 percent of colorectal cancer patients will be MSI-high. In earlier stages of cancer, it's estimated to be 5 percent or less.

Q And you would agree that MSI-high colorectal cancer subtype of cancer is relatively rare, correct?

A It's relatively rare as opposed to MSS patients. It's essentially 1 out of 10 patients with metastatic colorectal cancer is MSI-high. If that -- if you define that as relatively rare, then it meets the definition.

Q Well, would you agree that, in your understanding of what people in the art consider relatively rare to mean, that terminology would be applicable?

MS. BROWN-MARSHALL: Object to the form of the question.

A So to me, that's a bit of a vague question. I could answer the question by saying there are rare alterations that drive colon cancer, such as NTRK mutations, that's about 2 percent of patients. About

3 percent of patients have a mutation in HER2. 5 to 15 percent of patients have MSI-high tumors than -- that's less rare than some of these other mutations that are still relevant in management for colorectal cancer patients.

Q Dr. Goldberg, can you turn to paragraph 55 of your declaration.

A I can. I have it in front of me.

Q If you look to the fourth line from the bottom, you testify, "To speed accrual in a group of patients with a relatively rare subtype of cancer, MSI-high tumors, they also recruited teams at collaborating institutions, including my own," correct?

A Correct.

Q So you would agree that MSI-high cancer is a relatively rare subtype of cancer, correct?

A As I so stated.

Q Because MSI-high cancer is relatively rare, patients for the MSI-high cohorts of the 2013 MSI-high study would have been tested for MSI-high before being put into those cohorts, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A The answer to that is no.

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

MS. BROWN-MARSHALL: Object to the form of the question.

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

After that, in order to be eligible for the study, a colorectal cancer patient had to be known to be MSI-high and a non-colorectal cancer patient had

to be known to be MSI-high. But at the time that the study initially opened, accrual could proceed before MSI status was known.

Q Dr. Goldberg, are you reading from a document?

A No. But I'm trying to be articulate.

Q Dr. Goldberg, you said that such a process could happen. Are you saying that the process you just described is what happened for the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I would refer you to Nils' expert testimony, which discusses this in detail.

Q What do you mean by that, Dr. Goldberg?

A Exactly what I said; he had a detailed report of this in his declaration.

Q Was Dr. Lonberg involved in the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't know if he was involved in it or

not.

Q So what was the basis for the answer you provided me a moment ago about how patients could have been enrolled into the 2013 MSI-high study without having been tested for their MSI-high status?

MS. BROWN-MARSHALL: Object to the form of the question.

A So it comes from reading the protocol and from reading the declaration about the protocol that Nils did.

Q What protocol are you referring to, Dr. Goldberg?

A The protocol written by The Johns Hopkins University group that provided the guidelines for the study that we participated in and which was reported in the New England Journal of Medicine, that protocol was filed with the National Cancer Institute ClinicalTrials.gov, and I believe it's an appendix to the New England Journal of Medicine article.

Q Where do you cite to the protocol you're referring to in your declaration?

A I'm not sure if I cited it, but it's the

study that the protocol I'm talking about is the NCI number that we looked up earlier, which I would have to look up. I'm not sure what page it's on. What you've been referring to as the Hopkins MSI study.

Q Did you review Dr. Lonberg's declaration in preparation for today's deposition, Dr. Goldberg?

A I did.

Q Do you have it with you today?

A I do not.

Q And when you're referring to a declaration by Dr. Lonberg, do you know which declaration you're referring to?

A I only know of one declaration that was provided to me by the Fish attorneys.

Q And it was provided to you before you prepared your declaration?

A No. It was provided to me within the last couple weeks, long after I had signed the declaration.

Q So are you saying that the protocol was written in such a way that it said no MSI-high testing was necessary until a cohort closed, and

after that MSI-high testing was necessary?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the protocol is a written document. Rather than me speculating on what it says, why don't we look at it.

Q Well, you told me a moment ago that your answer was based on the protocol and you were familiar with it. Are you no longer sure about how the cohorts were filled?

MS. BROWN-MARSHALL: Objection to the form of the question.

A Well, you keep asking me the same question. I keep giving you the same answer. It is likely that we could resolve it objectively if we looked at the protocol. But if you keep asking me the question, I'll keep giving you the same answer.

Q And what is that answer, Dr. Goldberg?

A Ask me the question.

Q Are you saying that the 2013 MSI-high study was conducted such that initially no MSI-high testing was conducted prior to placing patients into

respective cohorts and testing was only required after the MSS cohort closed?

MS. BROWN-MARSHALL: Object to the form of the question.

A So that's a very complicated question, and in the end I'm going to say no to it because I believe I could say yes if you split it into parts, but no when you combine it all together. Perhaps you should split your question into parts and I'll address each one individually.

Q Let's actually circle back to something you said a little while ago, Dr. Goldberg. You said that a patient could be placed into a respective cohort without previously having been tested for their MSI-high status, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A That's my understanding, yes.

Q I understand how you can say a patient would have been enrolled in the study before being tested for MSI-high status.

How could a patient have been possibly

placed into a cohort without knowing their MSI-high status?

MS. BROWN-MARSHALL: Object to the form of the question.

A So as I stated, the treatment with pembrolizumab for cohorts A and B was the same, and so it wasn't necessary to know the MSI-high status at the time of enrollment and initiation of treatment.

It was necessary to know the MSI-high status to correctly assign the patient to the MSS or MSI-high cohort. But that could be done after the patient signed consent after they initiated treatment, because it didn't make a difference in terms of treatment, but it did make a difference in terms of which group their outcomes would be analyzed in.

Q What if there was an adverse reaction to one of the cohorts?

MS. BROWN-MARSHALL: Object to the form of the question.

A So you mean an adverse reaction to the pembrolizumab?

Q If Merck or JHU determined that one of the cohorts was particularly susceptible to an adverse reaction, under the understanding of the protocol that you've laid out, they wouldn't be able to deal with that, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't understand your question. If a patient had an adverse reaction, the protocol had specifications on how to manage it, overseen by Dr. Le. And it wouldn't have mattered whether they were MSI-high or MSS; it would be managed the same way for adverse reactions regardless of that.

Q I'm going to share on the screen, Dr. Goldberg, what has been previously marked as Exhibit 1064.

MS. BROWN-MARSHALL: Counsel, is this exhibit also going to appear in the folder link in the chat?

MR. ZEILBERGER: We can put it there.

MS. BROWN-MARSHALL: That would be helpful. Thank you.

THE TECHNICIAN: This is the remote technician. Counsel, is that something you're sharing on your own screen? I do not have a 1064.

MR. ZEILBERGER: Yes, we're going to share that now.

THE TECHNICIAN: Thank you.

BY MR. ZEILBERGER:

Q Can you see my screen, Dr. Goldberg?

A I do.

Q Do you see a PDF document that has a title "Supplemental Appendix" and at the bottom right it says Exhibit 1064?

A I see that.

Q And on the cover page of Exhibit 1064 it says it is a supplement to Le, et al., PD-1 blockade in tumors with a mismatch-repair deficiency, New England Journal of Medicine 2015?

A I see that.

Q And is this the supplement to the New England Journal of Medicine article that you were referring to earlier today?

A I can't tell yet what the text is about. I

can only see the title.

Q Sure. Turning to the next page, do you see the table of contents of this document?

A I do.

Q Do you have an understanding from the table of contents what this document is?

A My understanding is that this is not the clinical trial protocol, but, rather, a summary of the overall study design and some of the results of the study.

Q Do you have an understanding as to whether this document accurately reflects the design of the study?

MS. BROWN-MARSHALL: Object to the form of the question.

A I have not had an opportunity recently to review this supplementary appendix. When I look at the table of contents, all I see is Figure S1 is overview of study design. I assume that that is just a short summary in figure form of the study design, not an explication of the entire protocol.

Q Would you or other authors on the New

England Journal of Medicine article have submitted a supplement to that article that is not accurate?

MS. BROWN-MARSHALL: Object to the form of the question.

A I certainly wouldn't have submitted something that was inaccurate. But I cannot guarantee that something inaccurate wasn't presented by somebody else.

Q Turning to the fourth page of the PDF, it's numbered page 3 at the bottom -- can you still see my screen?

A I can.

Q Do you see how the second sentence under the header Patients says "All patients underwent MRR status testing prior to enrollment"?

A Let me just read that.

So I see that, but that is different than what I understood.

Q The explanation about patients undergoing MMR status testing prior to enrollment is inconsistent with the understanding you had when you prepared your declaration. Is that right?

MS. BROWN-MARSHALL: Object to the form of the question.

A So it does not state here that all patients' MMR status was known at the time that they were enrolled. And that was my understanding, was that patients could be enrolled regardless of whether they were known to be MSI-high or MSS.

Q So you're saying that patients would have been tested prior to enrollment, but the results of that test wouldn't have been looked at --

MS. BROWN-MARSHALL: Object to the form of the question.

Q -- until after the patients were placed into the cohort?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I don't see in this paragraph that it states that patients were -- had to be assigned to cohort A or cohort B prior to enrollment.

What it states here is an MMR status was tested. It doesn't say that it was used to assign the patients to arm A or arm B.

It seems like we have a pause here. In the next few minutes I would like to request that we take another break.

Q Sure, we can take a break.

(Recess 11:10 a.m. - 11:17 a.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, your opinions in your declaration are based on the understanding the priority date of the '393 patent is July 10th, 2015, correct?

A Correct.

Q Do you understand what a priority date is?

A I believe so. But would you like to explain it to me?

Q I would like to know your understanding of what a priority date is, Dr. Goldberg.

A So my understanding is that the priority date is the initial registration of an intent to patent an idea that sort of plants a flag in the sand stating that this idea is an invention that we intend to submit a patent for.

Q Before the alleged priority date of the

'393 patent, immuno-oncology agents were in development by laboratory and clinic-based research teams, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A Correct.

Q Why were immuno-oncology agents being developed?

MS. BROWN-MARSHALL: Object to the form of the question.

A You would have to ask the companies that were putting resources into doing that.

Q So you have no knowledge as to why before the alleged priority date of the '393 patent immuno-oncology agents were being developed?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the answer to your question is no.

Q So what is your understanding?

A Well, we don't --

MS. BROWN-MARSHALL: Sorry. Object to the form of the question.

A So there has been a tremendous interest over many years of trying to harness the immune system to kill cancer cells and decades of work and hundreds of careers have been devoted to trying to do that.

Up until the time that nivolumab was found by BMS investigators to be effective in some cancers, this work had largely been done in vain. Once there was a breakthrough with the findings about nivolumab being able to uncloak tumors so that T cells could recognize them as foreign and destroy them, there was an intense interest in the possibility of harnessing the immune system by developing additional PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, and other immunomodulating treatments in order to potentially further the ability to exploit innate immunity to destroy cancer cells. And so companies all over the world began more aggressively researching immuno-oncology opportunities once the first breakthrough had occurred.

Q And you understand that this first breakthrough you are referring to involving nivolumab

occurred before the alleged priority date of the '393 patent, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I know that nivolumab was approved for indications prior to 2015.

Q When you refer to a first breakthrough involving nivolumab, what are you referring to?

A Well, as I understand it, it was the first PD-1 inhibitor that showed activity, it showed activity in a number of different cancer types originating from different organs and it led to a patent and an FDA indication in several tumor types.

Q We looked at a little earlier today at paragraph 11 of your declaration, footnote 2 you refer to Exhibit 1005 to this proceeding, correct?

A Give me a moment, please.

Okay. So I have paragraph 11 in front of me. Please repeat your question.

Q In footnote 2 to paragraph 11 you refer to Exhibit 1005, correct?

A Correct.

Q And that is the MSI-high study record publicizing the 2013 MSI-high study, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So this references to the posting on ClinicalTrials.gov of Trial NCT01876511. That posting is required by the federal government for any clinical trials that are underway in the United States, so that's my understanding of what that footnote refers to.

Q Is ClinicalTrials.gov a secret website?

MS. BROWN-MARSHALL: Object to the form of the question.

A Frankly, that seems like a ridiculous question. It's ClinicalTrials.gov, it's open to anybody who puts ClinicalTrials.gov into their browser.

Q And it's fair to say that postings on ClinicalTrials.gov are publicly available. Yes?

MS. BROWN-MARSHALL: Object to the form of the question.

A As I stated, anybody who puts

ClinicalTrials.gov into their website -- their web browser, can go to that site.

Q And do you have Exhibit 1005 available to you right now?

A I don't have it. I don't know if Casey has it.

Q It should be in the folder that we've uploaded materials to, if it can be downloaded.

THE TECHNICIAN: This is the remote technician. Doctor, if you click on the link in the chat, that should take you to a browser window and the file should be available there.

A Okay. So I have clicked on that Planet Depos website and I see four PDFs. Which one are we referring to? Or three PDFs.

Q It should be labeled Exhibit 1005.

A I don't see that labeling.

THE TECHNICIAN: It may start with IPR202400240 and then EX1005.

THE WITNESS: Okay. Now I see it. Thank you. So it's loading.

A Okay. I have that in front of me now.

Q If you can please turn to page 3 of Exhibit 1005.

A Okay. I'm on page 3.

Q On page 3 Exhibit 1005 teaches that a study would be conducted to examine whether pembrolizumab is effective and safe in treating patients with MSI positive colon cancer, correct?

MS. BROWN-MARSHALL: Objection; mischaracterizes the document.

A Well, I see the brief summary. I'll read what it says on the brief summary.

It says, "This study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include patients with MSI positive colon cancer, patients with MSI negative colon cancer, and patients with other MSI positive cancers." That's what I see on this page.

Q In preparing your declaration, did you analyze what had been published in the art before the alleged priority date of the '393 patent regarding

the treatment of MSI-high cancer with immunotherapy including anti-PD-1 drugs?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I can't say that I read every bit of literature that had ever been published with regard to the use of PD-1 inhibitors in the treatment of cancer. I did read selected references.

Q Did you identify the references that you reviewed or were they provided to you?

A I did PubMed searches of relevant articles and considered those articles in formulating my declaration. I cited the ones that I specifically drew information from in the declaration.

Q When preparing your declaration, were you aware that before July 10th, 2015, including in 2014, there was published literature recognizing that effective immunotherapy for the treatment of colorectal cancer may be used in the near future?

MS. BROWN-MARSHALL: Objection to the form of the question.

A So I don't really know how to answer that

question. Was I aware that people thought that immunotherapy might work in cancer? Yes. That it might work in colon cancer? Yes. Was I aware of any data that it worked in colon cancer? No.

Q Were you aware that before July 10th, 2015, including in 2014, there was published literature recognizing that colorectal cancers associated with microsatellite instability were good candidates for immunotherapy?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I think somebody could have speculated that they were good candidates for immunotherapy. But until you do the experiment of treating human patients with immuno-oncology drugs, all that is is speculation.

Q I'm asking you, Dr. Goldberg, if you were aware of such publications when preparing your declaration.

MS. BROWN-MARSHALL: Object to the form of the question.

A Not that I recall.

Q And so you didn't consider any such publications when you prepared your declaration, correct?

MS. BROWN-MARSHALL: Objection; outside the scope of the declaration.

A So I'm not sure I really understand your question. Could you restate it, please?

Q When you prepared your declaration for this proceeding, were you aware that before July 10th, 2014 -- 2015, including in 2014, there was published literature recognizing that colorectal cancers associated with microsatellite instability were good candidates for immunotherapy?

MS. BROWN-MARSHALL: And I'm going to object, again, as outside the scope of the declaration.

A So I was not aware that there was any data -- (technical interruption).

MR. ZEILBERGER: I can no longer hear Dr. Goldberg. I don't know if other people can.

MS. BROWN-MARSHALL: No, counsel. I think the screen froze.

MR. ZEILBERGER: Okay. Why don't we go off the record while those technical issues are being resolved for Dr. Goldberg.

MS. BROWN-MARSHALL: I think they're back.

THE WITNESS: Okay. So I can see you and I can hear you. I don't know if you can hear me.

MR. ZEILBERGER: I can hear you now, Dr. Goldberg. And I think likely the vast majority of your answer was cut off, so I'll re-ask the question.

THE WITNESS: Okay.

BY MR. ZEILBERGER:

Q When you prepared your declaration for this proceeding, were you aware that before July 10th, 2015, including in 2014, there was published literature recognizing that colorectal cancers associated with microsatellite instability were good candidates for immunotherapy?

MS. BROWN-MARSHALL: Objection; outside the scope of the declaration.

A So I was not aware of any data that showed that any immuno-oncology intervention was effective

against colorectal cancer, whether it was MSI-high or MSS, and I was not specifically aware of any speculation that it was likely to be a good candidate for that.

Q Are you familiar, Dr. Goldberg, with the World Journal of Gastroenterology?

A I didn't get all of your question. All I heard was "World Journal of Gastroenterology."

Q I'll repeat the question. Are you familiar with the World Journal of Gastroenterology?

A I have not read that journal, so I believe it may exist, but I have not looked at it specifically.

Q And in preparing your declaration, you weren't provided any materials from the World Journal of Gastroenterology for consideration. Is that right?

MS. BROWN-MARSHALL: Object to the form of the question.

A Not that I recall.

Q Do you recall if you reviewed any literature published by Dr. Brunet (phonetic)?

MS. BROWN-MARSHALL: Object to the form of the question.

A That name is not familiar to me.

Q Were you aware that before July 10th, 2015, including in 2014, there was published literature recognizing that anti-PD-1 or PD-L1 antibodies are emerging as promising anti-cancer therapeutics?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I had not read any literature that I recall that promoted that idea.

Q In preparing your declaration, did you review any literature by Dr. Champiat?

A The name doesn't seem familiar to me. I can't remember the author's names of every bit of literature that I reviewed. But I don't remember that one specifically.

Q Is it fair to say that if you had been aware of literature recognizing that anti-PD-1 antibodies are emerging as promising anti-cancer therapeutics, you would have addressed it in your declaration?

MS. BROWN-MARSHALL: Objection to the form of the question and outside the scope of the declaration.

A It's hard for me to answer that question; it's a hypothetical question. And, you know, I know what I did to prepare for my declaration and I believe I was thorough in my preparations.

Q When you referred to data earlier, that you hadn't been aware of any data relating to the use of anti-PD-1 drugs for MSI-high cancer, what are you referring to by "data"?

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, there certainly was no human data that I was aware of.

One of the difficulties in the development of immuno-oncology drugs is that mouse models, which traditionally can be used for other classes of drugs, such as cytotoxics, are not relevant because the human immune system is peculiar to the human species. And so I wasn't aware of any preclinical data and I wasn't aware of any human clinical trial data.

The difficulty with immuno-oncology agents is that they have to be tested in humans because there are no laboratory models that predict how humans will respond to this class of drugs.

Q So are you saying that without any human data, all potential treatments are on equal footing?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't know how to answer that question. I guess the answer would be no, because you're saying all human -- all treatments would be on the same footing. Obviously that's not the case.

Q What would make somebody want to conduct a clinical trial involving a particular anti-PD-1 drug?

MS. BROWN-MARSHALL: Object to the form of the question.

A That's an incredibly broad question. I'll answer it with a broad answer. We don't cure cancer in all patients, and, therefore, people who are studying cancer are motivated to test every avenue that they can to try and improve the outcomes for our patients.

Q There is -- there are non-human trial-related reasons why a scientist would want to focus on a particular drug for a clinical trial, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I'm finding your questions very hard to answer because they're very convoluted and they seem off topic to me. Perhaps I'm missing something. You're certainly not referencing my declaration anymore, which is what I thought we were here to do.

Q I would appreciate it, Dr. Goldberg, if you could just answer my questions.

A Well, I would appreciate it if you would ask me questions that were answerable.

Q Is it your opinion that without human data, all drugs are equally speculative in terms of whether they will be effective?

MS. BROWN-MARSHALL: Objection; outside the scope of the declaration.

A No.

Q What will make a drug -- strike that.

Were you aware that before July 10th, 2015, including in 2014, there was published literature observing that emerging data confirmed that colorectal cancer is a heterogeneous group of tumors that can be divided -- subdivided by their molecular features and treated differently, including based on a tumor's status as microsatellite instable versus microsatellite stable?

MS. BROWN-MARSHALL: Object to the form of the question.

A Can you break that question up into single clauses that I can respond to? Because, you know, I have -- it's hard for me to respond to a complicated question like that with a cogent answer.

Q Were you aware that before July 10th, 2015, including 2014, there was published literature observing that emerging data confirmed that colorectal cancer is a heterogeneous group of tumors that can be subdivided by their molecular features?

A Yes, I'm aware of that.

MS. BROWN-MARSHALL: Objection.

Q Were you aware that before July 10th, 2015,

including in 2014, there was published literature observing that emerging data confirmed that colorectal cancer could be treated based on a tumor's status as a microsatellite instable versus microsatellite stable?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the data that I'm aware of was that in my clinical practice I treated patients at that time regardless of their microsatellite instability or stability with the same drug and the same drug strategies.

So even though it was known in 2015 that MSI-high tumors often were less responsive to conventional chemotherapy and existing targeted therapies, there were no alternatives to using those existing chemotherapies and targeted therapies. So patients with MSI -- MSI status of a tumor was irrelevant to treatment decisions at that time.

Q Were you aware that before July 10th, 2015, including in 2014, there was published literature observing that as a result of the intriguing data

from the nivolumab CRC study, clinical trials of anti-PD-1 agents were underway in patients with MSI-high colorectal tumors?

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, obviously I was aware that clinical trials were in progress for MSI-high -- for MSI-high colorectal cancer patients because I was participating in one.

Q Were you aware that there was literature specifically referencing intriguing data from the nivolumab colorectal cancer study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So one of the major references that I was aware of was the study published in the New England Journal, Topalian, which is referenced in my declaration, reporting on the experience of close to 300 patients treated with nivolumab having different types of cancers. And I'm aware that of the patients with colorectal cancer cited in her New England Journal article there were no responses.

I was also aware of the fact that some additional patients with colorectal cancer were treated with nivolumab, and of the 33 colorectal cancer patients treated, there was one response.

So that's the knowledge that I have regarding the efficacy of nivolumab in colorectal cancer up until that time.

Q When you prepared your declaration, were you aware of literature hypothesizing that tumors deficient in mismatch repair may be particularly sensitive to immunotherapy given an ongoing accumulation of mutations at a high frequency?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I was aware that mismatch repair defects that are indicated by microsatellite instability result in mutations in patients with mismatch repair deficient tumors. I was not aware that there was any data showing that that led to efficacy in human trials up until the Le study.

Q So I'm going to share in the chat a file Exhibit 1115, and I'll note this is a new exhibit and

we have labeled it as Exhibit 1115 for purposes of this deposition.

Please let me know when you have it, Dr. Goldberg.

A So when I opened the file I couldn't find it, so I'm going to refresh and see if it comes up now.

Q Sure.

A So I see three exhibits; one is called Test Exhibit, one is 1005, that we've already talked about, and the other is 2090. Those are the three things that I can see in my chat. I believe that's not -- none of those three are the things -- is the file that you would like me to look at.

Q I think the tech on the line is going to help you get access to it.

THE TECHNICIAN: Yes, sir. If you refresh your page, it should show up for you. If it's a large file; it may take a moment.

A So I just closed the exhibits and went back to the chat and reopened Exhibits 12, 13, 20, 24. I'll do that again. Okay. Now there's a fourth file

which is 1115. Is that the one that you would like me to open?

Q That's right.

A Okay. All right. I have that file open.

Q This document is titled "Recent Therapeutic Advances in the Treatment of Colorectal Cancer," correct?

A That's what it says.

Q Do you recognize this article?

A I do.

Q You are a co-author on this article, correct?

A Correct.

Q And on the cover page it indicates that this first published in a review in Advance on October 9th, 2014, correct?

A Yes, I see that.

Q Can you please turn to the second page of this PDF.

A Okay. That's page 2 of 13.

Q Correct. In the introduction to Exhibit 1115 it says that "The Cancer Genome Atlas project

and other efforts, discovery of new predictive biomarkers from clinical studies, and novel targeted agents introduced into clinical practice. Emerging data confirm that CRC, despite similar histology across cases, is a heterogeneous group of tumors that can be subdivided by their molecular features and treated differently, e.g., microsatellite instable versus microsatellite stable," correct?

MS. BROWN-MARSHALL: Objection; mischaracterizes the document.

A I see the statement that you're making.

Q What emerging data referenced in the introduction of this article that you co-authored were you referring to?

A So, clearly, the heterogeneity of colorectal cancer was something that was increasingly well-understood around 2014 when this was discovered. Some of the different drivers of colorectal cancer included microsatellite instability, RAS mutation, RAF mutation, PI3 kinase mutations. Some of those were amenable to treatment with specific targeted drugs; some were not.

And I think that this sentence talks about two things; heterogeneity and treatment distinctions. But not every one of the items listed under -- after the e.g. applies to both heterogeneity and differences in treatment. And microsatellite instability was not relevant to treatment decisions until after the discoveries by the Hopkins group.

Q And when you say after the discoveries of the Hopkins group, are you referring to a discovery on July 10th, 2015?

MS. BROWN-MARSHALL: Object to the form of the question.

A I'm referring to the discoveries made by the completion of the Hopkins trial that Dr. Le was running that we've been discussing in detail today.

Q You said that microsatellite instability was not relevant to treatment decisions until after the discoveries by the Hopkins group. Would you agree that microsatellite instability was relevant in considering potential treatments to be explored for microsatellite instable colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of

the question.

A Can you please (technical interruption.)

MR. ZEILBERGER: I think we've lost Dr. Goldberg again. Counsel?

MS. BROWN-MARSHALL: Yeah, I'm here. I can't see them either.

MR. ZEILBERGER: Okay. Let's go off the record while this is worked out.

(Pause in proceedings.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, can you hear me now?

A I can.

Q You said earlier that microsatellite instability was not relevant to treatment decisions before the alleged priority date of the '393 patent, correct?

A Yes.

Q Would you agree that microsatellite instability was relevant prior to the alleged priority date of the '393 patent in considering potential treatments to explore with clinical trials for microsatellite instable colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I would say that experiments testing new treatments and new combinations of treatments for microsatellite unstable tumors in patients was an unmet medical need that needed further investigation.

I'm not sure if I'm answering your question, but your questions are hard to answer because of so many dependent clauses.

Q What don't you understand about my question, Dr. Goldberg?

A Well, can you -- can you simplify your question so that it has a noun, a verb and a subject without a bunch of dependent clauses in it? I'm trying my best, but it's taxing to try and answer questions that are made up of sentences that are 20 pages long with "ands" in the middle of them.

Q I'd like to help you, Dr. Goldberg, but -- maybe I can repeat my question and maybe you can tell me what the clauses are that you're not understanding. Is that okay?

A Let's try it and see if we can make it

work.

Q Would you agree that microsatellite instability was a relevant factor prior to the alleged priority date of the '393 patent in considering potential treatments to explore with clinical trials for microsatellite instable colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I guess I'm going to say yes, and I'm going to paraphrase my understanding that there were unmet needs for the treatment of patients with MSI-high tumors, and, therefore, it was useful to explore new options for treatment for that group of patients.

Q If you could turn to page 8 of 13 of Exhibit 1115 and please let me know when you're there.

A Okay. I'm on page 8.

Q At page 8 your article has a section titled Immunotherapy in Colorectal Cancer, correct?

A Yes.

Q And the first sentence to that section says, "Within oncology, perhaps the most exciting current trend in developmental therapeutics is immunotherapy," correct?

A I see that.

Q Why did you describe immunotherapy as perhaps the most exciting current trend in developmental therapeutics?

A So it was based primarily on the data from the Topalian trial showing a high response rate in patients with refractory melanoma, a high response rate in patients with refractory non-small cell lung cancer, responses in bladder cancer, Hodgkin's lymphoma. Melanoma at that time was essentially refractory to all other treatment options, including cytotoxics and targeted therapy. And so to see a double digit response rate in refractory patients in that setting was extremely exciting but preliminary.

Q A little further in this paragraph of Exhibit 1115 your article says, "Unfortunately, immunotherapy in unselected patients with CRC has been largely disappointing thus far. However, it may

be that selected CRC patients will benefit from immunotherapy, and the challenge resides in discovering predictive biomarkers for this group of patients."

Do you see that?

A I do.

Q Why does the article say that it may be that selected CRC patients will benefit from immunotherapy?

MS. BROWN-MARSHALL: Object to the form of the question.

A Because we believe that there was the potential for immunotherapy to be effective. It just hadn't been shown to be yet.

Q And was that understanding based on the Topalian study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I would like to go down to references 49 and 50 here. I don't remember what we cited as 49 and 50, but that's the reference for that. So these references -- so 49 is a phase 1 study of single

agent PD-1 inhibitors in refractory solid tumors that were published in the Journal of Clinical Oncology in 2010. And then durable cancer regression off-treatment and effective reinduction therapy with a PD-1 inhibitor from Cancer Research, published in 2013.

So this was preliminary data from phase 1 studies, and I don't recall whether there were colon cancer patients included in these phase 1 -- in references 49 and 50 without going back to the papers.

Q You start the sentence that cites to references 49 and 50 by referring to a patient with refractory colorectal cancer, correct?

A Yes. And I believe that that may have been the patient in the Topalian study, the 1 out of 33 that responded, but I'm not certain.

Q Nivolumab is an anti-PD-1 inhibitor, correct?

A Yes, as stated in that sentence.

Q Based on the discussion in this paragraph of Exhibit 1115, there was human data relating to

anti-PD-1 drugs for an MSI-high colorectal cancer patient before July 10th, 2015, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So this paragraph references a single patient who had a sustained and deep response to nivolumab.

Q Is that not human data?

A That is human data.

Q Earlier today when you said that there was not any human data before July 10th, 2015 relating to the use of an anti-PD-1 drug for MSI-high colorectal cancer, that was not correct, true?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony.

A So this shows that there was data in one patient.

Q And you also explain specifically in this paragraph at page 8 of Exhibit 1115 that "Further analysis demonstrated this patient's tumor manifested high microsatellite instability with cell surface expression of PD-L1 by infiltrating macrophages and

lymphocytes," correct?

A That's what it states and it references reference 51.

Q And so you would agree that before the alleged priority date of the '393 patent, it was already publicly known that there was human data showing a durable complete response in a patient with MSI-high colorectal cancer through the treatment of an anti-PD-1 inhibitor, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So in the Topalian trial it showed that there was one patient of 33 who had responded to nivolumab, so there was an N of one finding that a single patient had responded to nivolumab at that time and that's what led to the Hopkins study.

Q And it was also publicly known that that patient had specifically MSI-high colorectal cancer, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A That's what it states in this article.

Q And that publicly known result is what led you to say in this article that it may be that selected colorectal cancer patients will benefit from immunotherapy, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So that led us to speculate that it might be true, but nobody had proven it. And I would remind you that both Merck and BMS were given the opportunities to support the Hopkins trial and they didn't feel that this one person's response was compelling enough to commit resources to test that.

Q The answer you just gave me, Dr. Goldberg, that's not based on any personal knowledge of yours, correct? That's based on what the JHU scientists told you?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony. Also asked and answered.

A And it's based on what I read in the Forbes article and the discussions that we have already covered with the JHU scientists.

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

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

MS. BROWN-MARSHALL: Counsel, is now a good time to take our lunch break?

MR. ZEILBERGER: Just a few more minutes, if that's okay with Dr. Goldberg.

THE WITNESS: That's fine.

Q In the paragraph that we're on right now, you say that "Given that immune checkpoint inhibitors work best in tumors with high mutation burdens, it is hypothesized that tumors deficient in mismatch repair such as this patient's cancer may be particularly sensitive to immunotherapy given an ongoing accumulation of mutations at a high frequency," correct?

A Yes, I see that.

Q When you used the word "hypothesized" there, is there a reason why you used the word "hypothesized" and not "speculated"?

A Because by this time we were participating

in the Hopkins trial and the hypothesis of the Hopkins trial is exactly as stated here.

Q You would agree, though, that there's a difference in scientific literature between the word "hypothesis" and "speculate," correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So a hypothesis is a kind of speculation, but it's a kind of speculation for which you can design an experiment to provide an answer.

Q Would you agree that the hypothesis you're referring to in Exhibit 1115 was based on at least some data supporting the hypothesis?

MS. BROWN-MARSHALL: Object to the form of the question.

A The hypothesis was based on the clinical trial that we were participating in being run by Hopkins, which was based on the response in one patient in the Topalian trial, who was subsequently found to be MSI-high.

Q When you say the word subsequently found to be MSI-high, you do understand that it was publicly

known that that patient was MSI-high, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A That is not my understanding. My understanding is that Dr. Diaz speculated that that patient was MSI-high. That patient was from Detroit. They went back to the patient's physicians, asked for a sample of the tumor. The tumor was then tested for microsatellite instability. And as Dr. Diaz had speculated, the patient was MSI-high, leading to the development of a hypothesis that MSI-high tumors might respond to PD-1 inhibitors and the development of a clinical trial that we have been discussing today.

Q So I'm going to share on my screen what's been previously marked as Exhibit 1057, and the tech can provide access to it to the extent you want to see it, the full file, but it is part of the record.

A So that will just show on my screen? Or what do I need --

Q Yeah, you should be able to see what I'm sharing right now.

A On the Zoom screen, okay. So a paper by the Hopkins group with the senior author being Dr. Topalian.

Q And this is the -- one of the two articles that you reference in your paper, correct?

A Correct.

Q And the first author is Dr. Lipson?

A I see that.

Q And if we scroll down to page 2 of 8, at the bottom right of the screen there is a section titled Durable complete response in colorectal cancer. Do you see that?

A I see that.

Q And it describes a 71-year old colorectal cancer patient who -- I'll stop there. Describes a 71-year old male with colorectal cancer, correct?

A I see that.

Q And at line 5 of that section, it explicitly identifies that this patient had microsatellite instability high genotype, correct?

A I see that, but it doesn't state when that discovery was made.

Q Understood, Dr. Goldberg. But do you see at the bottom right of the screen next to the page number, that this exhibit, this article was published on January 15th, 2013?

A I see that.

Q So as of January 2013, it would have been publicly known that the patient in the nivolumab study who had a complete response had MSI-high colorectal cancer, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A Correct.

MR. ZEILBERGER: Okay. Why don't we take a break.

THE WITNESS: What time are we going to resume?

MR. ZEILBERGER: We can go off the record.

(Recess 12:27 p.m. - 1:00 p.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, looking back to Exhibit 1115, do you have that?

A I have to pull it up again. That was the

one we were just working with, right?

Q The one just before the one we were looking at most recently.

A Okay. So I have 1115 in front of me. We were on page 8, correct?

Q Yes. Thank you. The last sentence in the section directed to immunotherapy in colorectal cancers says, "As a result of these intriguing data, clinical trials of anti-PD-1 agents are currently underway in patients with MSI-high colorectal tumors," correct?

A I see that.

Q Why did you call out MSI-high colorectal tumors in that sentence as opposed to MSI-low colorectal tumors?

MS. BROWN-MARSHALL: Object to the form.

A So the point of this was we were discussing the Hopkins trial that we were participating in.

Q Where do you mention the JHU study here?

A We don't, but that was why we made this statement.

Q And it's your opinion that the JHU study

that you're referring to was intended to assess MSI-high colorectal tumors?

MS. BROWN-MARSHALL: Object to the form of the question.

A If you read the hypothesis and the protocol, it specifically states that it's an experiment being done to assess the effect of PD-1 inhibitors in MSS colorectal cancer, MSI-high colorectal cancer, and MSI-high non-colorectal cancer.

Q Right. And you just mentioned MSS colorectal cancer, whereas in your article at page 8 you don't mention MSS colorectal cancer, correct?

A That's correct. But I also don't mention brain tumors or anal cancer or all kinds of things. I mention what I mention. I don't mention what I don't mention.

Q Are you saying that MSS colorectal cancer has the same relevance to immunotherapy in colorectal cancer as brain cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A The relevance of PD-1 inhibitors in a variety of different cancers was not understood at this time.

Q Was there intriguing data for the use of anti-PD-1 agents in patients with MSS colorectal tumors?

MS. BROWN-MARSHALL: Object --

A Well, the data that existed was the Topalian study where one of 33 patients responded. I'm not aware that they tested the microsatellite instability status of the other 32 patients. But I am aware that they tested one patient who responded, as we discussed before the break, and that that patient's tumor was MSI-high.

Q So you were not aware of any data that was intriguing with respect to the use of anti-PD-1 agents for patients with MSS colorectal tumors, correct?

A So I would say correct, but that was an unresolved question that was tested in arm B of the Hopkins trial.

Q But it's fair to say that the reason why

you specifically mentioned MSI-high colorectal tumors in your article is that that is what the intriguing data was related to. Yes?

MS. BROWN-MARSHALL: Object to the form of the question.

A The intriguing data was related to the one 71-year old man from Detroit who responded to nivolumab.

Q And you're referring to the patient who was tested as MSI-high colorectal cancer, correct?

A I'm referring to the patient who responded to nivolumab, who had colorectal cancer and whose tumor turned out to be MSI-high.

MR. ZEILBERGER: Okay. Can the tech please share, not on the screen, but share the file Exhibit 1117.

A So will that be put in the chat or on the screen, on the Zoom screen?

Q It should be put into the chat location.

THE TECHNICIAN: And to clarify, counsel, I do not believe I have access to 1117, unless it's been provided in an alternate method.

Correction, I see it now. One moment, please. It is uploading to the folder now.

A Okay. I have 1117 open in front of me.

Q And this is a document we have newly marked as Exhibit 1117. It's not previously part of the record.

Do you recognize this document, Dr. Goldberg?

A I see that it says that it is the protocol that we have been discussing that was published in the Le paper and that it was referenced in the Le paper.

Q And you have previously reviewed this protocol, correct?

A Not recently.

Q When you prepared -- or when you were involved in the preparation of the New England Journal of Medicine article that you just referenced, at that time you would have reviewed this protocol?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I reviewed this protocol when I was

participating in it, but that was almost a decade ago.

Q Can you please turn to page 40 of 226 to Exhibit 1117.

A Okay. It will take a minute to scroll down. Okay. I have page 40 in front of me.

Q Page 40 is a study calendar, correct?

A Yes.

Q And there is a pre-study period of time, correct?

A I see that.

Q And then following the pre-study period, there is a 14-day cycle, correct?

A Correct.

Q And then following the 14-day cycle, there is a 20-week period of time, correct?

A Correct.

Q And then following the 20 weeks it goes to off study, correct?

A Correct.

Q Under the pre-study period of time, one of the agenda items is informed consent, correct?

A Yes. So I'm noticing at the bottom of this page that it says Original Version 1.1 May 30, 2013. Is this the original version?

Q Are you asking, Dr. Goldberg, if this -- I'm not sure I understand your question, Dr. Goldberg.

A Do you see at the bottom of the page under "Tumor Biopsies," are you with me?

Q Yes, Dr. Goldberg.

A It says "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable Tumors Original Version 1.1 May 30, 2013." I didn't notice the date of this document and I'm not sure if it's at the top. I can go back and look.

Q Well, let's stick with this page for now, Dr. Goldberg.

A Well, that's a critical question because the protocol may have been amended and I don't know whether this was the original version or a new version.

Q I would like to understand how you interpret this version of the protocol, Dr. Goldberg.

Under the pre-study period of time another agenda item is inclusion/exclusion criteria, correct?

A Yes.

Q Another agenda item under pre-study is demographics, correct?

A Can you refer me where in the protocol you're looking? Are you still on page 40?

Q Yes.

A So I don't see -- I see inclusion/exclusion criteria under pre-study, that's what you're referring to?

Q And I just asked you about the next item, demographics.

A Okay. I see that.

Q And under demographics is MSI testing, correct?

A I see that.

Q And MSI testing is also part of the pre-study period of time, correct?

A That's what it states here.

Q So assuming the protocol was conducted in accordance with what is provided under the study

calendar at page 40 of Exhibit 1117, MSI testing would have been conducted during the pre-study period of time, correct?

MS. BROWN-MARSHALL: Object to the form of the -- Dr. Goldberg, let me get my objection on the record.

Object to the form of the question.

A So that's why I asked whether this was the original version of the study or an amended version of the study.

As you'll recall, at the time that Ohio State activated the study, all patients who needed to be accrued to the MSS arm of the trial had been accrued. And so in order for a patient to be eligible after that cohort had been filled, they would have had to have MSI testing performed pre-study, because if they were MSS, they were no longer eligible. But my -- I'm unsure whether this is the original version or a later version.

Q So if you turn to page 2, Dr. Goldberg, that might help you. Or at least we can start there. Page 2 indicates that this supplement, and this is a

supplement to the New England Journal of Medicine article, contains the original protocol, the final protocol, and the summary of changes, correct?

A I see that.

Q And if you turn to page 4 of 226, under Protocol Type it indicates Original then Version 1, May 1, 2013, and under that Original/Version 1.1 May 30th, 2013, correct?

A I see that.

Q Does that help you understand whether the protocol that we are looking at is the original version?

A I believe that that answers the question. Thank you.

Q Turning back to page 40 of Exhibit 1117.

A Give me a minute to get there. Okay.

Q You would agree, then, that even in the original version of the protocol, before you got involved in the study, MSI testing was conducted pre-study, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So it specifies here that the testing needed to be done, but it doesn't specify that the results needed to be known.

Q Would it have been logical, Dr. Goldberg, for a study protocol to specifically require MSI testing to be pre-study and then not look at those results pre-study?

MS. BROWN-MARSHALL: Object to the form of the question.

A So MSI testing is not a same day turnaround study. MSI testing can be done several different ways; one way is immunohistochemistry and another way is PCR. Neither of those turn around quickly. They end up oftentimes having to be sent to an outside lab to be done, and so the reporting may be several days or even weeks later than the ordering of the test.

Q Page 40 of the protocol Exhibit 1117 doesn't say that MSI testing was conducted same day, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A Can you point to what you're looking at on

that page? Or would you --

Q Let me ask it -- let me rephrase my question.

The pre-study period of time is not a single day, correct?

A The pre-study checklist, eligibility checklist has to be filled out before a patient can be enrolled in the study. But the studies do not have to be conducted on the same day.

Q If we look at the visit windows, the very first row, there's a 28-day period for the pre-study window, correct?

A You're back on page 40?

Q I never left page 40, Dr. Goldberg.

A So I'm now back on page 40 and it says that there's a 28-day period before enrollment during which studies can be conducted, and that often is done to accommodate imaging studies, which are expensive and which you don't want to repeat unless it's necessary.

Q And that also could have been done to accommodate MSI testing, correct?

A It could, but not necessarily would.

Q Is it fair to say that you don't know one way or the other whether that's how it was in fact done in the 2013 MSI-high study?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't see any data on this page that tells me whether it was done before -- whether the MSI testing results would have been available before the patient was enrolled and treated.

Q And all I'm asking you, Dr. Goldberg, is to confirm whether -- you don't know one way or the other whether MSI testing was done for the 2013 MSI-high study during the pre-study period?

MS. BROWN-MARSHALL: Object to the form of the question.

A So what I understand is that the MSI testing had to have been ordered, but I don't know if it was resulted before the patient was enrolled and treated, according to what is stated here.

Q Okay. Let's turn back to your declaration, paragraph 54.

A Okay. I'm on paragraph 54.

Q In the first sentence you say, "The finding that PD-1 inhibitors had the potential to be an active agent for a subset of patients with colorectal cancer was unexpected," correct?

A It states that.

Q When you say that the discovery was unexpected, that is from the perspective of the time period before the MSI-high study record published, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So my understanding is the MSI study record the NCI. -- NCI ClinicalTrials.gov document?

Q No, Dr. Goldberg. I'm referring to the 2013 MSI-high study protocol that published as Exhibit 1005 on June 10th -- or in June of 2013.

MS. BROWN-MARSHALL: Counsel, that was not what you said in your original question. Please be more consistent.

MR. ZEILBERGER: Counsel, Dr. Goldberg asked me to clarify my question. Please don't

mischaracterize the record.

A So, again, I'm confused a little bit. Please just ask me the question again so I can reconsider it.

Q I can rephrase it.

When you say in paragraph 54 of your declaration that the discovery was unexpected, that is from the perspective of before June 2013 when the 2013 MSI-high study record published, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the problem that I'm having is when the MSI study record published. So at the time that we enrolled in this trial, the trial was confidential, it wasn't in the public domain. It was filed -- the experimental plan was filed at NCI -- at ClinicalTrials.gov, but the entire protocol was not available there, at least I don't think it was.

Q Parts of the protocol were published on ClinicalTrials.gov, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't know that. Can you show it to me?
Q You were looking at it earlier, Dr. Goldberg. It's Exhibit 1005, which you had pulled up already earlier. If you want to refer to it again, you're more than welcome to.
A Okay. I'm going to go back and refer to it again just so that I'm sure I know what I'm talking about. So I have it in front of me, it's a six-page document, most of which is blank, and it has a study description, which I previously read. This study will be looking at whether pembro is effective in three different patient populations. So that, as I understand it, is what was published in this document, not the clinical protocol.
Q Can you turn to paragraph 52 of your declaration, please.
A Okay.
Q At the end of that paragraph you say that [as read] "CRC is not associated with known mutagen exposure and therefore those tumors would not likely have the high mutational burden and high level of mutation associated with neoantigens that predict

that PD-1 inhibitors will work in melanoma and small cell lung cancers," correct?

A I see that.

Q Is MSI-high colorectal cancer associated with high mutational burden?

MS. BROWN-MARSHALL: Object to the form of the question.

A MSI-high colorectal cancer is a small subset, as we've established, in colorectal cancers, and MSS colorectal cancers are not MSI-high. And in either circumstance, mutagen exposure is not understood to be applicable to carcinogenesis in the colon.

Q Do I need to repeat my question, Dr. Goldberg? I don't believe you answered it.

A Please repeat it.

Q Is MSI-high colorectal cancer associated with high mutational burden?

MS. BROWN-MARSHALL: Objection; asked and answered.

A MSI-high colorectal cancer is not associated with mutagen exposure, but it is

associated with a high level of neoantigens.

Q Did I ask you about mutagen exposure?

MS. BROWN-MARSHALL: Objection; argumentative.

A That's in the sentence that you're referencing.

Q And when I asked you is MSI-high colorectal cancer associated with high mutational burden, you answered that it's not associated with mutagen exposure, but it is associated with a high level of neoantigens.

Are you agreeing or disagreeing that MSI-high colorectal cancer is associated with high mutational burden?

MS. BROWN-MARSHALL: Objection; asked and answered.

A So I guess I should say please refer to my prior answer, which is a part of the record.

Q I would like an answer to my question, Dr. Goldberg.

MS. BROWN-MARSHALL: Objection; asked and answered.

A Please refer to my prior answer to the same question.

Q What is that answer, Dr. Goldberg?

MS. BROWN-MARSHALL: Objection; asked and answered.

A Can the reporter read it back to us?

Q I have the text of your answer, Dr. Goldberg. That's not the issue.

You're refusing to say whether or not MSI-high cancer is associated with high mutational burden. Are you able to answer that with a yes or no?

MS. BROWN-MARSHALL: Objection; asked and answered.

A So the problem that I'm having is that you referred me to paragraph 52 of my report, which has a sentence that has an "and" in it, and the mutagen exposure is relevant to the statement that I made about the fact that CRC would be a less interesting target for ongoing study of the PD-1 inhibitor.

So if you would like me to answer the question outside of the context of that statement in

my declaration, I will tell you that, yes, MSI-high colorectal cancers have a high mutational burden.

Q Is it your opinion that before the alleged priority dates of the '393 patent, it was not known that MSI-high colorectal cancer was associated with high mutational burden?

MS. BROWN-MARSHALL: Object to the form of the question.

A No.

Q Are you saying no, that's not your opinion, or no, it was not known?

A Please restate your question.

Q Is it your opinion that before the alleged priority dates of the '393 patent, it was not known that MSI-high colorectal cancer was associated with high mutational burden?

MS. BROWN-MARSHALL: Object to the form of the question.

A It is my opinion that it was known that high mutational load was associated with MSI-high colon cancer. I don't know why you put a "not" in your sentence other than possibly to confuse me.

Q Keytruda was approved for advanced melanoma before the alleged priority date of the '393 patent, correct?

A Yes.

Q Even by 2010, word began to filter through to Merck that nivolumab was showing signs of promise, correct?

MS. BROWN-MARSHALL: Objection; outside the scope of the declaration.

A I've had no contact with Merck so I have no idea what they knew.

Q And you didn't review any documents that dealt with what Merck knew in 2010?

MS. BROWN-MARSHALL: Object to the form of the question.

A I reviewed the Topalian paper, which recounted the nivo study that she and the Hopkins team did for -- in collaboration with BMS. I did not review any Merck documents or reports of Merck's knowledge or lack of knowledge of mechanisms of action.

Q Did you review any documents that discussed

Merck's knowledge of mechanisms of action?

MS. BROWN-MARSHALL: Object to the form of the question.

A The introduction to the Topalian study discusses the mechanisms of action of PD-1 inhibitors, and I reviewed that paper.

Q Were you aware that in 2010 Merck reactivated IND development for pembrolizumab?

MS. BROWN-MARSHALL: Object to the form of the question.

A I was not aware of that. I was not aware that they had inactivated IND development.

MR. ZEILBERGER: Can the tech please share as a file Exhibit 2051.

THE TECHNICIAN: Please stand by. The file is uploading now.

A Please repeat the name of the file.

Q It's Exhibit 2051.

A It hasn't yet uploaded for me.

THE TECHNICIAN: If you refresh your page, Doctor, does it appear now?

THE WITNESS: 2051. Okay. Yes, I see it.

A That's the Forbes article.
Q This is the Forbes article that you mentioned earlier, correct?
A Correct.
Q And it's an article that you cite in your declaration, correct?
A Correct.
Q And you reviewed this article and relied on it for your declaration?
A I did review this article.
Q And you relied on it for your declaration?
A I don't remember when I reviewed it, whether it was before the declaration or later.
Q Can you please turn to page 7 of Exhibit 2051.
A Okay. I'm on page 7.
Q And in the first full paragraph the Forbes article indicates that everything changed, however, by the middle of 2010, correct?
A I see that sentence.
Q And towards the bottom of that same paragraph, it says that "word began to filter through

to Merck that nivolumab, or nivo (brand name: OPDIVO), an earlier-stage molecule targeting PD-1 that BMS also acquired," it says "though" but I think it should say "through its recent acquisition of Medarex, was showing signs of promise," correct?

A I see that.

Q Before I just brought this to your attention, you were not aware of this information. Is that right?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I read this article, but I read many articles in preparation for this, and I did not remember every sentence of every article that I read.

Q And in the next paragraph of Exhibit 2051, "From what was literally a standing stop, Merck urgently reactivated IND development in mid-2010, targeting a filing by the end of the year and achieving it in December," correct?

A I see that.

Q When you prepared your declaration, were you aware that in 2010 Merck had reactivated IND

development of Keytruda?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I remember reading this paragraph, and part of the reason I remember that is Eric Rubin was the oncologist who took care of my mother when she had ovarian cancer, but I didn't remember the details of the IND development by Merck.

Q And if we look towards the bottom of page 7, the Forbes article indicates that "The results from the melanoma cohort were striking," and that's referring to Merck's melanoma cohort, correct?

MS. BROWN-MARSHALL: Objection; mischaracterizes the document.

A I see the sentence that "The results from the melanoma cohort were striking."

Q So you disagree that that relates to a Keytruda melanoma cohort?

MS. BROWN-MARSHALL: Objection to the form of the question.

A I can't tell what it refers to. In the next sentence it refers to a pembro study and the

quote from Dr. Ribas.

Q I see. So it's your understanding that Keytruda and pembro are two different things?

MS. BROWN-MARSHALL: Object to the form of the question.

A Let me just read. I'm going to start in the paragraph above to try and get better context here.

Okay. Now I understand this better, having read the paragraph above. So ask me your question again, please.

Q The melanoma cohort that is referenced as having striking results at the bottom of page 7 relates to a Keytruda cohort, correct?

A Correct.

Q And Keytruda is the brand name for pembrolizumab, correct?

A Correct.

Q And if you go on to page 9 of Exhibit 2051.

A Okay. I'm on page 9.

Q The Forbes article indicates that "Merck scientists involved in the program tell me they

needed little prodding from Ribas, saying they were acutely aware of both the potential clinical utility of their drug and the commercial need to close the gap with a competitor who seemed to be years ahead."

Do you see that?

A Yes. Let me just read it again.

Okay. I see that sentence.

Q Do you have an opinion on whether -- well, strike that.

Do you agree or disagree with the statement in the Forbes article that the Merck scientists were acutely aware of both the potential clinical utility of their drug and the commercial need to close the gap with a competitor who seemed to be years ahead?

MS. BROWN-MARSHALL: Objection; outside the scope of the declaration.

A So I neither disagree or agree with the statement that Mr. Shaywitz made. I accept that he fact checked his statements before he made them.

Q Can you turn back to your declaration, please.

A Okay. What paragraph?

Q Can you turn to paragraph 58.
A Okay. I have that in front of me.
Q You note in paragraph 58 how Keytruda obtained breakthrough therapy designation for the treatment of patients with MSI-high colorectal cancer, correct?
A I see that sentence, yes.
Q You don't mention how Keytruda had received an earlier breakthrough therapy designation for advanced melanoma, correct?
A My report focuses on colorectal cancer.
Q So it's your opinion that the earlier breakthrough therapy designation for Keytruda for advanced melanoma was not relevant?
MS. BROWN-MARSHALL: Objection --
A Not relevant to what?
MS. BROWN-MARSHALL: Object to the form of the question.
A Was not relevant to what?
Q To the use of Keytruda for MSI-high colorectal cancer.
MS. BROWN-MARSHALL: Object to the form of

the question.

A So if you look at the keynote series of studies that Merck has done, their first success was in melanoma, and then they ran clinical trials in at least a dozen other tumor types. So the relevance to doing those studies was they saw a good result in one of kind of tumor and they wanted to run experiments to see if that good result could be replicated in other tumors.

They didn't make the assumption, nor would the FDA allow them to, that success in one kind of cancer treatment would be translatable to other types of cancer treatments without running a trial.

Q What document were you referencing, Dr. Goldberg, in providing that answer?

MS. BROWN-MARSHALL: Objection. Object to the form of the question.

A I was referencing my experience as an expert witness, not a document.

Q I can see you're looking at a document, Dr. Goldberg, so I would just like to know what you're looking at. I can't see it. Your screen

blurs it.

A My declaration. It is the only document that I have in front of me. You asked me to look at paragraph 52 in the document, so I was following your orders.

Q Would you agree that nivolumab was the first PD-1 inhibitor that was developed?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't know the answer to that. I know it was the first PD-1 inhibitor to get an FDA approval, but I'm not sure -- there are many PD-1 inhibitors and I'm not sure of the timeline of their development.

Q I see. So if you go up to paragraph 50 of your declaration, would you amend your first sentence to refer to FDA approval?

MS. BROWN-MARSHALL: Object to the form of the question.

A I think it would be reasonable to amend it because the rest of the paragraph talks about the clinical trial that led to the evidence that the FDA

considered in approving the study. Laboratory development and clinical development are two different things, and I was referring to clinical development.

Q If you go down to paragraph 53.

A Okay.

Q Four lines from the bottom you refer to a patient's -- the sensitivity of a patient's tumor to pembrolizumab. Do you see that?

A Let me read the sentence.

I see that.

Q Would you agree that's a mistake?

A No.

Q So which responding CRC patient are you referring to in paragraph 53?

A The 71-year old man treated on the Topalian study, that was the one patient out of 33 patients treated with nivo who responded to nivolumab and who had subsequent MSI testing done to show that that patient was MSI-high.

Q Are you saying that nivolumab and pembrolizumab are the same thing?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony.

A Of course not.

Q So what did you mean when you refer to sensitivity of that patient's tumor to pembrolizumab?

A So that actually is a misstatement. It should have been nivolumab.

Q Is there a reason why when I asked you earlier if it was a mistake, you said no?

MS. BROWN-MARSHALL: Objection; argumentative.

A I did not read the full sentence.

Q When -- strike that.

Do you have an understanding as to why the JHU scientists did not want to conduct their study using nivolumab?

MS. BROWN-MARSHALL: Objection. Object to the form of the question.

A So as I understand it from what I have been told by the JHU scientists, they first approached BMS with their study proposals to test a PD-1 inhibitor in MSI-high colon cancer and BMS declined to support the study.

So they then went to Merck and made the same pitch and had the same response; Merck declined to support the study. But Merck eventually agreed to provide the drug without additional monies to support the study at the time the study was initiated.

Q What is your understanding as to why the JHU scientists went to BMS first to try to use nivolumab?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I think you'll have an opportunity to depose the JHU scientists and you can ask them directly.

My supposition is that the one patient who had responded had been treated with nivo, so they wanted to test that in a larger sample of patients.

Q What is your understanding as to why the JHU scientists went to Merck second to try to use pembrolizumab?

MS. BROWN-MARSHALL: Object to the form of the question.

A For the same reason I just stated. There

was a response in that one 71-year old man to nivolumab, and they wanted to extend the experience of treatment with a PD-1 inhibitor in MSI-high colon cancer, it would make sense to extend the experience in a circumstance where a patient had already been treated with that drug and shown a response.

Q But why would the JHU scientists have specifically picked pembrolizumab as their second choice as opposed to a different PD-1 inhibitor?

MS. BROWN-MARSHALL: Object to the form of the question.

A You're going to have to ask the JHU scientists that question.

Q Is that because you don't know the answer to the question?

MS. BROWN-MARSHALL: Object to the form of the question.

A I can speculate, but I wasn't a part of the discussions or the solicitations of the drug companies for support.

Q What would be your speculation?

MS. BROWN-MARSHALL: Object to the form of

the question.

A My speculation is that they really wanted to test the hypothesis that PD-1 inhibitors would work in MSI-high patients. And when they couldn't get support from BMS, they looked for another source of a PD-1 inhibitor and therefore went to Merck.

Q Is it fair to say that the prior breakthrough therapy designation for pembrolizumab would have played a factor in whether the JHU scientists wanted to use pembrolizumab for their study?

MS. BROWN-MARSHALL: Object to the form of the question.

A You keep asking me what the JHU scientists were thinking. I did not participate in these deliberations, nor was I a part of their solicitations for support or for access to drug.

Q Would the prior breakthrough therapy designation for pembrolizumab have played a factor for a person of ordinary skill in the art in deciding which PD-1 inhibitor to use for the study?

MS. BROWN-MARSHALL: Object to the form of

the question.

A No.

Q So you're testifying that, all else being equal, a person of ordinary skill in the art would have considered a PD-1 inhibitor that has no prior approvals on equal footing with a PD-1 inhibitor that has prior approvals?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony.

A I didn't say that.

Q Can you please explain your answer of "no" then?

MS. BROWN-MARSHALL: Object to the form of the --

(Simultaneous speaking.)

MS. BROWN-MARSHALL: Dr. Goldberg, let me get my objection.

Object to the form of the question.

A Nivolumab had prior FDA approval and pembrolizumab had prior FDA approval, so both were drugs that had a record of benefit in other tumor types and both should be considered for testing of a

new hypothesis, such as the ability of a PD-1 inhibitor to be of benefit to patients with MSI-high tumors.

Q You understand, Dr. Goldberg, that there were other PD-1 inhibitors in existence before the 2013 MSI-high study started that had no prior approvals. Yes?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I don't have specific knowledge of what PD-1 inhibitors besides pembro and nivo were under development, but I suspect that there were multiple PD-1 inhibitors under development based upon the subsequent studies that have occurred after that time.

Q And the fact that pembrolizumab was one of the PD-1 inhibitors that had received an approval for an indication would have played a factor in deciding which PD-1 inhibitor to use for the study, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A Again, you keep asking me to tell you what

the Hopkins team thought, and I was not a part of their deliberations.

Q I'm not asking you what the Hopkins team thought, Dr. Goldberg.

I'm asking what a person of ordinary skill in the field would have thought at that time, whether they would have factored this.

MS. BROWN-MARSHALL: Object to the form of the question.

A So a person of ordinary skill in the art, who wanted to test the hypothesis that a PD-1 inhibitor would be beneficial to patients with microsatellite instability high tumors, would look at the universe of PD-1 inhibitors, would look at their progress and development and the clinical experience with them, and would likely pick the agent or agents for which there was the most experience because they would be well-characterized with regard to toxicity and tolerability.

Q Now, you say in your declaration that both BMS and Merck were not willing to fund the study, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I say that on the basis of communications with the Hopkins team and having read the Forbes article.

Q What is your understanding, then, on why the study was ultimately performed using pembrolizumab and not nivolumab?

MS. BROWN-MARSHALL: Object to the form of the question.

A So my understanding is that BMS was unwilling to provide their drug and Merck was willing to provide their drug.

Q Do you have an understanding as to why Merck was willing to provide their drug?

MS. BROWN-MARSHALL: Object to the form of the question.

A I never had any direct conversations with Merck about pembrolizumab.

Q Do you have an understanding from anyone as to why Merck was willing to provide their drug?

MS. BROWN-MARSHALL: Object to the form of

the question.

A So I had conversations with the Hopkins team and I read the Forbes article.

Q Do you have an understanding from your conversations with what you call the Hopkins team or the Forbes article as to why Merck was willing to provide their drug?

A I don't understand -- I don't have an opinion as to why they were. I only have an opinion or I can only recognize the fact that they did provide it.

Q Can you go back to paragraph 49 of your declaration, and please let me know when you're there.

A Okay.

Q In the last sentence of paragraph 49 you say, "Prior to JHU's clinical trial that demonstrated that PD-1 inhibitors were effective in treating MSI-high/dMMR solid tumors, PD-1 inhibitors had failed to be effective in treating CRC cancers," correct?

A That's what it states.

Q The nivolumab study that successfully treated one patient with MSI-high colorectal cancer occurred prior to JHU's clinical trial that you reference in paragraph 49, correct?

A That's correct.

MS. BROWN-MARSHALL: Counsel, we have been going for over an hour. Would now be a good time to take at a break?

MR. ZEILBERGER: I think it's been just about an hour.

Q But, Dr. Goldberg, did you want to take a break?

A You know, this is a long process, and I think an hourly break is a reasonable thing to do on a regular basis.

Q No problem. I just wanted to make sure you wanted a break. Happy to take a break. You just need to let me know.

A Okay.

MR. ZEILBERGER: Let's go off the record.

(Recess 2:06 p.m. - 2:17 p.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, can you please go to paragraph 61 of your declaration.

A Okay.

Q In paragraph 61, in the second sentence you say, "While pembrolizumab is a PD-1 inhibitor like nivolumab had been tested in a group of patients with MSS tumors, it is a different drug." Do you see that?

A Yes. So there's a -- the word "that" should be present in that sentence between "nivolumab" and "had been."

Q So you're saying in the sentence that both pembrolizumab and nivolumab had been tested in a group of patients with MSS tumors. Is that right?

MS. BROWN-MARSHALL: Object -- object to the form of the question.

Q Can you please explain what you meant in this sentence?

A Nivolumab is a PD-1 inhibitor that had been tested in a group of patients with MSS tumors. While pembrolizumab is also a PD-1 inhibitor, it is a different drug.

Q Why do you say that nivolumab had been tested in a group of patients with MSS tumors?

MS. BROWN-MARSHALL: Object to the form of the -- object to the form of the question.

A So it had been tested in the Topalian study in 33 patients with colorectal cancer. We don't know the microsatellite stability status of all of those patients, but you would predict at least 85 percent of them would have been MSS.

Q Isn't it true that the only status of a patient in the Topalian study that you do know is MSI-high?

MS. BROWN-MARSHALL: Object to the form of the question.

A So the only patient whose microsatellite instability tumor status that I know of is that of the 71-year old man. I don't know if Topalian and colleagues had MSI testing results on other patients.

And so what I am stating is that since 85 percent or more of patients with colorectal cancer are MSS, regardless of whether they had been tested, the majority of the patients enrolled in the Topalian

study would have been MSS based on statistics.

Q In paragraph 61 you don't say a majority of the patients would have had MSS tumors, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I'm saying that now. I didn't say it in there.

Q You agree -- would you agree that the Topalian study that you referred to showed that nivolumab is not effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So since I don't know the MS -- the microsatellite status of the patients in the Topalian study, I can't say specifically.

But as I stated just a moment ago, the vast majority of those patients with colorectal cancer who are unselected with regard to microsatellite instability status would have likely been MSS, and only one of 33 responded.

Q A person of ordinary skill in the art

reading the Topalian study would have thought that nivolumab is not effective for treating MSS colorectal cancer, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So, again, there was no data presented on the microsatellite status of the tumors in the patients who were enrolled in the Topalian study. So I'm not sure that a POSA would make any conclusion with respect to differentiating MSI-high from MSS patients for that cohort.

Q Dr. Goldberg, you differentiated in paragraph 61 where you said nivolumab had been tested in a group of patients with MSS tumors, did you not?

MS. BROWN-MARSHALL: Objection; asked and answered.

A So I'll go through it again. 85 percent of patients with colon cancer at least are MSS. This was a group of 33 patients. The high likelihood is about 25 percent of them or more -- or 25 of those 33 or more would have been MSS.

So, indeed, nivolumab was tested in a

cohort of patients who were MSS, but I'm not certain of the individual patients' MSS status.

Q I wasn't asking you if you're certain about the individual patients' MSS status.

I asked you whether a person of ordinary skill in the art reading the Topalian study would have thought that nivolumab is not effective for treating MSS colorectal cancer.

A I believe that they would have concluded that, yes, based on the logic that I've provided repeatedly and in my status as a POSA.

Q In paragraph 61 you go on to say that "it was important to independently test pembrolizumab's potential for benefit in mCRC patients with MSS tumors," correct?

A Yes.

Excuse me just a minute. The lights just went out on me. I think I'm going to move my seat because I think the sensor doesn't know that I'm at the end of the table.

Q No problem.

A I'm situated now. Can you ask me the

question again, please.

Q There's no question pending yet. I had asked you about the sentence in paragraph 61 where you say that "it was important to independently test pembrolizumab's potential for benefit in mCRC patients with MSS tumors." Do you remember me pointing you to that?

A Yes, I see that sentence.

Q Was there anything about pembrolizumab that was known at the time that would have suggested it would be effective for MSS tumors where nivolumab was not effective?

MS. BROWN-MARSHALL: Object to the form of the question.

A So we're talking about two drugs. They are drugs that are in the same class. They're both PD-1 inhibitors. But when we have multiple drugs in a drug class, we don't make any assumptions about whether because one is active or inactive, the other is going to be inactive or active. The test has to be done with that drug in that population.

Q I'm not asking you about assumptions,

Dr. Goldberg. I'm asking you whether there was anything about pembrolizumab that was known at the time that would have suggested it would be effective for MSS tumors where nivolumab was not effective?

MS. BROWN-MARSHALL: Objection; asked and answered.

A So I can't really state the universe of knowledge about pembrolizumab, much of which was proprietary at that time. So I believe the drug needed to be tested, so did the Hopkins investigator team and the IRBs that determined the ethical considerations with regard to entering patients on a trial of pembrolizumab in MSS patients did not object to it because the efficacy was unknown at that time.

Q Under what theory was it thought that pembrolizumab may be effective for treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't really know how to answer that. Pembrolizumab hadn't been tested in this setting, and therefore the only way to know whether it was

effective or not was to conduct the experiment.

Q You would agree I, assume, Dr. Goldberg, that drugs are not given at random in the hopes that they treat a random illness?

MS. BROWN-MARSHALL: Object to the form of the question.

A Again, you put "nots" in there and it makes it hard to understand the question that you're asking. Could you ask it as an affirmative question rather than as a negative question, please?

Q Clinical trials are conducted to test a hypothesis, correct?

A Correct.

Q Under what hypothesis would pembrolizumab have been effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A Pembrolizumab had not been tested in MSS colon cancer. Therefore, one could hypothesize that it could be effective, and the only way to know that for sure would be to treat some patients with it and

see if it was effective.

Q On what basis could one hypothesize that pembrolizumab could be effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Objection; asked and answered.

A Because it had not previously been tested in that setting.

Q Besides the fact that pembrolizumab had not previously been tested in the treatment of MSS colorectal cancer, is there any basis whatsoever to think that it would have been effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I can answer that from the perspective of today when we know that there are some patients with MSS colorectal cancer that respond to pembrolizumab.

In fact, there were several in Dr. Le's study that had tumor shrinkage who were MSS if you look at the curves from her New England Journal

Article, the swimmer plots from her New England Journal article.

We also know that other measures of tumor mutational burden, such as TMV, that are different than MSI-high testing, can predict more responses to PD-1 inhibitors in some circumstances. I don't believe that that was really well-understood in 2013, but it is understood now.

Q Besides the fact that pembrolizumab had not previously been tested in the treatment of MSS colorectal cancer, in 2013, what is your understanding as to the basis to think that pembrolizumab could have been effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Objection; asked and answered.

A I believe this is the fourth or fifth time you've asked me that question and I feel like I've answered it to the best of my ability. If you keep asking me the same question, I will give you the same answer, that I've already answered it to the best of my ability.

Q Dr. Goldberg, in the previous answer you gave me you specifically said, well, I don't know about 2013, but thinking about today.

The most recent question is about 2013. I know your counsel said asked and answered, which might have led you to give me the response you gave me, but I would like your answer.

MS. BROWN-MARSHALL: Is there a question pending?

MR. ZEILBERGER: There is, counsel.

A Can you ask the question, please?

Q Besides the fact that pembrolizumab had not previously been tested in the treatment of MSS colorectal cancer, in 2013, what is your understanding as to the basis to think that pembrolizumab could have been effective in treating MSS colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So unless a drug is specifically tested in a specific patient population, one cannot say whether it would be effective or would not be effective

without doing the study.

Q Turning to paragraph 60 of your declaration.

A Okay.

Q In the paragraph -- in the sentence bridging pages 39 and 40, you say, "Had the results of the trial been obvious before it was conducted, i.e. that it was obvious that the MSS cohort would not respond, it would have been unethical to construct such a protocol, let alone enroll patients to cohort B, and IRB would not have approved the trial," correct?

A I see the sentence as you read it.

Q What do you mean by "obvious" in that sentence?

A If there was no hope that there could be any benefit for a specific patient subgroup, it would be unethical to treat that subgroup with that particular intervention.

I'm going to get up because the lights in here are still flashing, I'm going to see if I can stop them --

Q No problem.
A Okay. I think I may have fixed it.
Q It would have been ethical to include the MSS cohort in the 2013 MSI-high study even if there was optimism that the MSI-high cohorts would respond well, correct?
MS. BROWN-MARSHALL: Object to the form of the question.
A The two cohorts are separate, and I don't see how it's relevant that how one cohort would respond would determine whether it was ethical to treat another cohort in a basket trial such as this.
Q So you agree that even if there was optimism about the MSI-high cohorts before the 2013 MSI-high study was conducted, that would not have made it unethical to include the MSS cohort, correct?
MS. BROWN-MARSHALL: Object to the form of the question.
A So 85 percent of patients with metastatic colorectal cancer are MSS and those patients die of colon cancer. So experiments to try and improve their outcomes was an unmet need and remains an unmet

need.

Q In the sentence you were just talking about, is it fair to say that you characterized the results of the trial as the MSS cohort not responding?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't understand the question. Could you please restate it?

Q In the sentence bridging pages 39 and to 40 of your declaration, you say, "Had the results of the trial been obvious before it was conducted, i.e. that it was obvious that the MSS cohort would not respond." Do you see that?

A I see that.

Q So you're describing in that sentence as one of the results of the trial, that the MSS cohort did not respond, fair?

A That the MSS cohort would not respond. The study hadn't been done yet, so nobody knew if they would respond or not.

Q Was one of the results of the 2013 MSI-high

study that the MSS cohort did not respond?

MS. BROWN-MARSHALL: Object to the form of the question.

A Well, if you look at the figures in the New England Journal of paper article, there were some patients who were MSS who had tumor shrinkage, but whose response was not sufficient to meet the NCI's definition of a partial response. You could argue that those patients had some benefit from the treatment even though they didn't meet the definition of a partial response. And actually, their duration of response was apparently prolonged -- their progression-free survival, to be more precise, was apparently prolonged in some circumstances in some individuals.

Q Separate from the MSS cohort, another one of the results of the trial was that the MSI-high cohorts did respond, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So not every patient whose tumor was MSI-high did respond. But some patients whose tumors

were MSI-high showed evidence of a response.

Q Are you disputing whether the MSI-high cohorts of the 2013 MSI-high study were successful?

MS. BROWN-MARSHALL: Object to the form of the question.

A Of course not. The fact that not every patient benefits doesn't take away from the fact that the patients who benefited got a positive result from it.

Q Okay. I didn't ask you whether every patient benefited, Dr. Goldberg.

If it was obvious before the MSI study was conducted that patients in the MSI-high cohorts would respond well to pembrolizumab, would you agree that that would not make it unethical to include an MSS cohort?

MS. BROWN-MARSHALL: Object to the form of the question.

A Another one of these convoluted questions with a "not" thrown in in the middle. Please try to restate your question in a way that --

Q Let's take it in parts, Dr. Goldberg.

First part. This is the premise. I want you to assume that before the 2013 MSI-high study, that it was obvious, before the 2013 MSI-high study was conducted, that patients in the MSI-high cohorts would respond well to pembrolizumab.

Are you with me?

A Well, I understand what you're saying, but why would I assume that? That hadn't been tested.

Q I'm asking you to assume it.

A Okay.

Q Are you able to assume it for purposes of this question --

A It is an incorrect assumption on the basis of history, but we'll pretend that that was the case.

Q With that assumption, even if that assumption was true, that would not make it unethical to include the MSS cohorts, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A I don't think it's relevant. There are two different cohorts of patients and the hypothesis needed to be tested in both cohorts. You don't in

oncology say, well, this works in one cohort of patients, so we're not going to test it in another cohort of patients who might benefit until you test it to see if they do.

Q But you agree with me that it would not be unethical to have the MSS cohort in that situation, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So I'm going to say I believe it would have been ethical today or back in 2013 to enroll patients with MSS colorectal cancer in this trial.

Q And it would have been ethical to enroll patients with MSS colorectal cancer in this trial in 2013 even if it was obvious that patients with MSS -- MSI-high -- excuse me. Let me start over.

It would have been ethical to enroll patients with MSS colorectal cancer in this trial in 2013 even if it was obvious that patients with MSI-high colorectal cancer would respond well, correct?

MS. BROWN-MARSHALL: Object to the form of

the question.

A I would say asked and answered. You have asked me this question four or five times. I assume you're hoping that I'll give you a different response, but I'm not going to.

It was ethical to enroll MSS patients even if the science would have suggested that MSI-high patients had a higher likelihood of response.

Q Can you please turn to paragraph 47 of your declaration.

A Okay.

Q Sorry, one moment.

In paragraph 47 you refer to "a new era in immune system-based cancer treatment," correct?

MS. BROWN-MARSHALL: Objection; mischaracterizes the document.

A I'll read you the sentence. "Their discovery and clinical development ushered in a new era in immune system-based cancer treatment."

Q Did I misread one of the words there, Dr. Goldberg?

A I read the words.

Q And you also refer to immuno-oncology agents, correct?
A Correct.
Q And this paragraph is under a section header labeled "No Effective Immuno-Oncology Treatments for CRC Prior to JHU's clinical trial," correct?
A That's -- yes, that's correct. It's item C in bold on page 30.
Q Are you saying that the long-felt need addressed by the '393 patent was a need for immuno-oncology agents for colorectal cancer?
MS. BROWN-MARSHALL: Object to the form of the question.
A Can you repeat the question, please?
Q Are you saying that the long-felt need addressed by the '393 patent was a need for immuno-oncology agents for colorectal cancer?
MS. BROWN-MARSHALL: Same objection.
A So yes, the '393 patent was a development that affected a subset of patients with colorectal cancer, but did not address the unfelt need for the

85 percent of patients who were not MSI-high or the approximately 50 percent of patients who are MSI-high who have no response to PD-1 inhibitors.

Q If you can turn back to paragraph 27.

A Okay.

Q In paragraph 27 you say, "In my opinion, Keytruda (pembrolizumab) and its microsatellite instability-high related FDA-approved indications, which embody the inventions claimed in the '393 patent, fulfilled a long-felt, but previously unmet need for an effective treatment for MSI-high colorectal cancer, with the most pressing need being treatments for metastatic colorectal cancer," correct?

A I see that sentence, yes.

Q So are you testifying that the long-felt need addressed by the '393 patent was a need for an effective treatment for MSI-high colorectal cancer?

A Please repeat the question.

Q Are you testifying that the long-felt need addressed by the '393 patent was a need for an effective treatment for MSI-high colorectal cancer?

A Yes.
Q When did the need for an effective treatment for MSI-high colorectal cancer materialize?
MS. BROWN-MARSHALL: Object to the form of the question.
A So there's been a need for treatment for MSI-high colorectal cancer since colorectal cancer was diagnosed. So I would assume it probably happened a millennia ago.
Q MSI-high colorectal cancer was diagnosed a millennia ago?
MS. BROWN-MARSHALL: Object to the form of the question.
A People had MSI-high colorectal cancer then; we just didn't know what it was. MSI-high, the microsatellite instability was discovered in the late 20th century.
Q For how long -- strike that.
Since when was it known that there could be a specific treatment for MSI-high colorectal cancer?
MS. BROWN-MARSHALL: Object to the form of the question.

A That was discovered in 2015 with the publication of the Le paper.

Q So are you saying that the Le paper addressed a need that people didn't know existed?

MS. BROWN-MARSHALL: Object to the form of the question.

A The short answer is no. That seems like a silly question.

Q So for how long did people know there was a need for a specific treatment for MSI-high colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A Since MSI-high colorectal cancer was discovered, there has been a need to treat it. And it was -- so Lynch syndrome was first suspected by Henry Lynch, for whom the syndrome is named, who is a clinical oncologist with genetics training, working at Creighton University in Omaha.

He took care of patients with large families, many of whom had multiple family members who died of colon cancer or endometrial cancer. He,

therefore, hypothesized that colorectal cancer could be the result of an inherited cancer susceptibility syndrome. He was not a laboratory scientist, so he did not elucidate the underpinnings of that from a molecular genetics perspective.

Later, laboratory investigators such as Albert de la Chapelle, who I mentioned earlier, who was at Ohio State, Bert Vogelstein at Johns Hopkins, and some investigators from Sweden elucidated the biologic abnormality of mismatch repair defect that is the causative genetic abnormality that results in Lynch syndrome and in some microsatellite high colorectal cancers.

Other patients with colorectal cancer, did not have an inherited genetic susceptibility, they acquire their mismatch repair defect for unknown reasons, probably some interplay between heredity, environment and exposures.

Q Still in paragraph 27, where you say "with the most pressing need being treatments for metastatic colorectal cancer," are you saying that the '393 patent addressed a long-felt need for

metastatic colorectal cancer?

MS. BROWN-MARSHALL: Object to the form of the question.

A So could we turn to the '393 patent that's cited later in my report so that I can refer to that? I'll look for it and see if I can find it.

On page 47 number -- paragraph number 74. Are you there?

Q Go ahead.

A So if you'll note in this claim 1 of the '393 patent, it makes no reference to the stage of colorectal cancer for which this invention is patented. It just states, "A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient." It doesn't state whether that human patient has stage 1, 2, 3 or 4 colorectal cancer.

Q Are you correcting the testimony you have in paragraph 27 where you say that the '393 patent fulfilled a long-felt, but previously unmet need for an effective treatment for MSI-high colorectal cancer with the most pressing need being treatments for

metastatic colorectal cancer?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony.

A I stand by that statement.

Q So you are saying that the '393 patent fulfilled a long-felt need directed to metastatic colorectal cancer?

MS. BROWN-MARSHALL: Objection.

A You're misrepresenting the sentence. Let me read the sentence to you.

"In my opinion, Keytruda and its microsatellite instability-high related FDA-approved indications, which embody the inventions claimed in the '393 patent, fulfilled a long-felt, but previously unmet need for effective treatment of MSI-high colorectal cancer."

Like the patent, I don't specify a stage in making that statement. But I add that the most pressing need was for metastatic colorectal cancer.

So from my interpretation of this sentence, it includes all patients with colorectal cancer, but it calls out those with metastatic colorectal cancer,

who virtually always die of their disease, as having the most pressing need.

Q I asked you whether you're saying the '393 patent fulfilled a long-felt need directed to metastatic colorectal cancer and you said I'm misrepresenting you.

So do you disagree with the statement that the '393 patent fulfilled a long-felt need directed to metastatic colorectal cancer?

MS. BROWN-MARSHALL: Objection; asked and answered.

A The '393 patent fulfilled a long-felt need for treatment of metastatic colorectal cancer.

Q Is it your opinion that it fulfilled a long-felt need for treatment of MSS metastatic colorectal cancer?

A If you read the FDA indication, it only includes patients with MSI-high colorectal cancer.

Q I'm asking you about the '393 patent, Dr. Goldberg.

A The '393 patent doesn't make any statement about MSS colorectal cancer, that I recall.

Q So when you refer to metastatic colorectal cancer in paragraph 27, are you referring to MSI-high metastatic colorectal cancer?

A I am.

Q You say in paragraph 27 that "Keytruda and its microsatellite instability-high related FDA-approved indications embody the inventions claimed in the '393 patent," correct?

A Right.

Q What is that opinion based on?

A Let me read the sentence again.

So can you ask the question again? I'm not quite sure what you're asking.

Q In paragraph 27 you say that "Keytruda and its microsatellite instability-high related FDA-approved indications embody the inventions claimed in the '393 patent." Is that correct?

A That's correct.

Q What is that opinion based on?

A It's based on the claim 1 of the patent.

Q What analysis did you do to compare claim 1 of the patent to Keytruda and its MSI-high related

FDA-approved indications?

A My declaration.

Q Can you please explain what you mean?

A I put together a 52-page report addressing that question.

Q You have 52 pages in your report directed to the issue of whether Keytruda and its MSI-high related FDA-approved indications are embodied in the inventions claimed in the '393 patent?

A I believe that that's what this declaration focuses on, yes.

Q Can you please turn to paragraph 51 of your declaration.

A Okay.

Q You observe in paragraph 51 that Merck conducted its own studies using pembrolizumab in melanoma in non-small cell lung cancer, correct?

A Correct.

Q And those studies by Merck were partially in response to BMS's experience with nivolumab, correct?

MS. BROWN-MARSHALL: Object to the form of

the question.

A So that is a logical conclusion, but I am not in touch with representatives from Merck to know exactly what their logic was.

Q Did you not believe this statement to be true when you included it in your declaration, Dr. Goldberg?

MS. BROWN-MARSHALL: Objection; argumentative.

A Of course I believed it to be true or I would not have put it in my declaration.

Q You go on to say in paragraph 51 that "The Merck studies in patients with melanoma and non-small cell lung cancer showed similar activity as that observed with nivolumab in these diseases," correct?

A Yes. That's references by Robert and by Reck that are noted at the bottom of the page.

Q Would a person of ordinary skill in the art have been surprised to see that pembrolizumab showed similar activity as nivolumab for patients with melanoma and non-small cell lung cancer?

A I believe they would not have been surprised, but they wouldn't have known whether that

was the case unless the experiment had been done.

Q They would not have been surprised because they have similar mechanisms of action, correct?

A Correct. But the FDA would not have approved pembrolizumab on the basis of BMS's experience without appropriate trials.

MR. ZEILBERGER: I think we have been going for about a break -- about an hour. Would you like a break?

THE WITNESS: Sure. We'll reconvene at 3:15?

MR. ZEILBERGER: Why don't we do 3:20.

(Recess 3:09 p.m. - 3:21 p.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, after the results from the nivolumab study published in 2013, is it fair to say that the development of treatments using PD-1 inhibitors for MSI-high cancer progressed rapidly?

MS. BROWN-MARSHALL: Object to the form of the question.

A As compared to what?

Q As compared to typical progress for cancer

treatment.

A So I would say --

MS. BROWN-MARSHALL: Object to the form of the question.

A It's fair to say that there was a great amount of interest, as was stated in the paper that Kristen Ciombor and I wrote and that we discussed earlier --

(Court Reporter clarification.)

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

Q Is it fair to say, then, that a person of ordinary skill in the art would have been optimistic enough about the MSI-high cohorts in the 2013 MSI-high study to want to obtain the data from that study?

MS. BROWN-MARSHALL: Object to the form of

the question.

A So I think we all wanted to know how well these worked and wanted to see studies done and to get the results of the studies as quickly as possible.

Q That is because there was some optimism about how these drugs would work, correct?

MS. BROWN-MARSHALL: Object to the form of the question.

A So as I said before, response rates in melanoma and non-small cell lung cancer patients, who had been previously treated in the double digits, was unprecedented and very exciting.

Q Before the break we were talking about the claimed invention. Do you remember that?

A I do. Can you refer me to a paragraph on the report, please?

Q Paragraph 27, where I guess you say in the opposite way, inventions claimed in the '393 patent.

A Okay.

Q When we talked about that before, you pointed me to claim 1 of the '393 patent, correct?

A Correct.

Q Is claim 1 of the '393 patent the only claim that you assessed for your declaration?

MS. BROWN-MARSHALL: Object to the form of the question.

A I read and assessed the entire '393 patent.

Q Can you please show me where you analyze any claims other than claim 1 of the '393 patent?

MS. BROWN-MARSHALL: Object to the form of the question.

A So from my perspective, claim 1 of the '393 patent is an umbrella claim, and the other claims of the patent are subsidiary to that umbrella claim. So I felt that by addressing claim 1, I was addressing the other claims within the patent.

Q In paragraph 71 of your declaration. Are you there?

A Yes.

Q In paragraph 71 of your declaration you say that "Prior to the May 2017 approval of the MSI-high indication, Keytruda was not approved for any indications that allowed for the treatment of

colorectal cancer patients. Practically, this meant that doctors would not prescribe Keytruda to CRC patients outside of the context of a clinical trial," correct?

A Correct.

Q So that it is your opinion that prior to May 2017, there would not have been any sales of Keytruda for the treatment of MSI-high colorectal cancer, correct?

MS. BROWN-MARSHALL: Objection; mischaracterizes the document.

A So as I understand it, Keytruda was on the market for the non-small cell and bladder and Hodgkin's disease and melanoma indications, and so a clinical oncologist could write a prescription for it.

Having said that, it was a very expensive drug and most patients couldn't afford to pay for it out of pocket.

As noted at the bottom of page 45, Merck may have had a compassionate use protocol. I don't know whether they did or not. But if they did, they

would have had to provide the agent free of charge to patients because they didn't have an FDA-approved indication.

Q Do you have an opinion as to whether there would have been any sales of Keytruda for the treatment of MSI-high colorectal cancer prior to May 2017?

MS. BROWN-MARSHALL: Object to the form of the question.

A So you represent Merck, you probably could ask them. I don't have specific knowledge of whether there were any sales or not.

Q Now, I understand you spoke to Mr. Segers about this proceeding, correct?

A He's the economic expert? Is that correct?

Q JHU holds him out as such, yes.

A I did have a conversation with him.

Q Did you provide any opinions to Mr. Segers?

A So that conversation was with two lawyers from Fish, and I don't know whether it's privileged. Can someone advise me about that?

MS. BROWN-MARSHALL: It's okay to answer

these questions. I'll caution you if you get close to privileged information.

A Okay. Mr. Segers did most of the talking. I mostly listened to what he had to say.

Q What did he have to say to you?

A He talked about the economic success of Keytruda sales and how that was a sign that it met one of the eight indicia that we specified earlier in this report.

Q And in what fashion did that impact your analysis in your declaration?

A I didn't address the economic success of this drug. I was asked to address the unmet need.

Q Are you saying, then, that the conversation you had with Mr. Segers was not relevant to your opinions?

MS. BROWN-MARSHALL: Objection; mischaracterizes previous testimony.

A My conversation with him was relevant to my understanding of the issues involved in this patent, but is not cited or referenced in my declaration.

Q Did you provide Mr. Segers with an

understanding about how or whether the claims of the '393 patent correspond with the use of pembrolizumab for its MSI-high indications?

A I do not have a memory of giving him any such information, no.

Q What information did you provide Mr. Segers?

A As I mentioned, I mostly listened to what he had to say.

Q I recall that, and I suppose I'm latching onto the word "mostly." Was there any information you provided Mr. Segers?

A I think we had some small talk. But I don't believe that I provided him any substantive information contained in my report. He was interested in telling me what he was opining on, not listening to what I was opining on, and that wasn't the purpose of the call.

Q And was it just a single call that you had with him? Or did you have any other conversations with him?

A I had a single call with him.

Q Going down to paragraph 73 of your

declaration.

A Okay.

Q In paragraph 73 you say, "An oncologist reviewing the Keytruda label would understand that a CRC patient treated under either of these indications would be treated in response to determining that that patient's tumor is either MSI-high or dMMR by testing the patient's tumor," correct?

A I see that statement.

Q What do you mean by "in response to" in that statement?

MS. BROWN-MARSHALL: Objection; calls for a legal conclusion.

A So the sense of this sentence is that an oncologist or a POSA reviewing the label would understand that they needed to do MSI testing to determine if the patient was likely to benefit or meet the indications for treatment with pembrolizumab.

Q So are you saying, then, that there would not need to be an MSI-high determination?

A I'm saying that there would need to be an

MSI-high determination.

Q In paragraph 77 of your declaration, if you could move forward a little bit.

A Okay.

Q You say in paragraph 77 that "there is a nexus between the claims of the '393 patent and the methods of treating MSI-high CRC according to the Keytruda label," correct?

A I see that sentence, yes.

Q When you use the word "nexus" there, what do you mean?

A Essentially, a connection.

Q What do you mean by "connection"?

A That the patent covers the invention of a method for treating patients with MSI-high colorectal cancer with pembrolizumab and I would say based on all of the information that we've exhaustively reviewed today.

MR. ZEILBERGER: Okay. Let's take a five-minute break.

MS. BROWN-MARSHALL: Okay.

(Recess 3:40 p.m. - 3:49 p.m.)

BY MR. ZEILBERGER:

Q Dr. Goldberg, have you ever developed a clinical trial on a novel cancer therapy?

A Yes.

MS. BROWN-MARSHALL: Objection; vague.

Q Which novel cancer therapy did you -- for which did you develop a clinical trial?

A There are multiple clinical trials that when I was at Mayo Clinic and University of North Carolina and Ohio State we had phase 1 programs that were testing first-in-man drugs, as well as first-in-man combinations, and I can't remember all the names of them. I don't have my CV in front of me, but I could pull it up and look at it, if that would be of use.

Q You said that -- you referred to "we" at your time at Mayo Clinic and the University of North Carolina, Ohio State. Did you personally develop those clinical trials involving novel cancer therapies?

A So we worked in teams and we rotated the responsibility of being the principal investigator on

clinical trials, but we participated in each others' trials and we participated in the monitoring of each others' trials.

Q Did you write the protocol for any of the trials you're referring to that involved novel cancer therapy?

A So I wrote a number of trials, yes.

Q Which therapies were they directed to?

A Well, let me pull up my CV so I can refresh my memory. This has been quite awhile ago. Is that all right?

Q That's fine.

A It's going to take me a minute.

MS. BROWN-MARSHALL: Maybe it would be easier, counsel, do you have his CV? It should be attached to his declaration. Do you have that as an exhibit?

MR. ZEILBERGER: Counsel, I believe you made it part of his exhibit. Did you not provide Dr. Goldberg with his full declaration today?

MS. BROWN-MARSHALL: So, Dr. Goldberg, do you have a physical copy of your CV with your

declaration, or do you just have the declaration itself?

THE WITNESS: I just have the declaration itself. But I have my CV up in a Word document. I just need to get to the relevant places on it. It will just take me a minute.

A Okay. So one of the studies that I had looked at was a drug called Octreotide, or somatostatin, in the treatment of patients with asymptomatic advanced colorectal cancer. This was done in 1995.

Let's see. I wrote a trial with a drug called fazarabine. Ara-AC is another name for it. This was in 1997.

Developed a phase 1 study of duocarmycin in patients with refractory cancers in 1998.

Do you want me to keep going?

Q Let's pause for a second. The drugs that you just listed, which I believe are somatostatin, fazarabine, and duocarmycin -- well, I guess, first, did I get those right?

A More or less, enough so that it's not worth

fussing with the names.

So somatostatin ended up being an approved drug. The other two were failures and were never -- never went beyond early phase testing.

Q With respect to somatostatin, was the trial that you conducted, did that lead to the approval of somatostatin?

A It did not --

MS. BROWN-MARSHALL: Object. Object to the form of the question.

A Somatostatin was not ever approved for treatment of colorectal cancer. It was approved for treatment of carcinoid tumors and neuroendocrine tumors, based on other studies that we did at Mayo Clinic, but not ones I was the principal investigator for.

Q Dr. Goldberg, during any of the breaks during today's deposition did you speak to anyone or receive any information whatsoever regarding this proceeding?

A I received no information. I spoke to Casey because we were in the same room and she was

leaving and so we had a social conversation, but it had nothing to do with proceedings that we have going on.

I did email a former patient during one of the breaks, but it had nothing to do with this.

MR. ZEILBERGER: Thank you very much for your time today, Dr. Goldberg. We have no further questions.

MS. BROWN-MARSHALL: Thank you, counsel.

EXAMINATION

BY MS. BROWN-MARSHALL:

Q Dr. Goldberg, I have just a couple questions for you.

Do you remember counsel asking you questions regarding the 2013 MSI-high clinical trial?

A I do. There were quite a lot of questions about that.

Q Okay. And what is your understanding of what the 2013 MSI-high clinical trial is?

A I believe that they were discussing the trial that we participated in run by Dr. Le and reported in the New England Journal in 2015.

Q Okay. And is that the clinical trial that's identified as NCT01876511?

MR. ZEILBERGER: Objection; leading.

A Give me a minute and I can give you the number. I believe it's -- that would be specified, I believe, in the ClinicalTrials.gov, which I guess I can pull up because it's in the folder. Is that correct?

Q Counsel -- sorry, Dr. Goldberg, I'm not sure what you're referring to. Let me re-ask my question.

A Okay.

MR. ZEILBERGER: I do want to make clear that the exhibits are still available. I think you might be referring to Exhibit 1005, Dr. Goldberg, and it should still be there for you.

A Okay. Let me just pull it up and I'll verify the number of -- the NCI.gov number of the trial.

So it's NCT01876511.

Q Okay. And looking at Exhibit 1005, do you see that there's a section called "Study Record

Versions"?

MR. ZEILBERGER: Objection; leading.

A I see a notation in the ClinicalTrials.gov archive where about halfway down the page it says "Study Record Versions," yes.

Q Okay. And what was the date of the first study record version for the clinical trial with NCT01876511?

A It states June 10th, 2013.

Q Okay. And what is the date of the last entry for the study record version for NCT01876511?

A The final one, number 28, was posted on February 4th, 2020 and is stated to be study status.

MS. BROWN-MARSHALL: Okay. No further questions.

THE WITNESS: Does that mean that we are concluded?

MS. BROWN-MARSHALL: Counsel can decide if they're going to ask any follow-up questions, so we're waiting for them.

MR. ZEILBERGER: Just take a quick two-minute break, if you don't mind.

MS. BROWN-MARSHALL: That's fine.

(Recess 4:01 p.m. - 4:04 p.m.)

MR. ZEILBERGER: Thank you again, Dr. Goldberg. We have no additional questions.

THE WITNESS: Okay. Thank you, everyone.

(Time noted: 4:05 p.m.)

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CERTIFICATE OF CERTIFIED SHORTHAND REPORTER

NOTARY PUBLIC

I, MONIQUE VOUTHOURIS, Certified Court Reporter and Notary Public within and for the State of New Jersey, do hereby certify:

That RICHARD M. GOLDBERG, M.D., the witness whose remote deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition, and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, THE JOHNS HOPKINS UNIVERSITY, was represented by counsel at the deposition.

I further certify that the deposition of RICHARD M. GOLDBERG, M.D., occurred remotely via Zoom Videoconference, on Friday, December 13, 2024, commencing at 9:05 a.m. EST to 4:05 p.m. EST.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way

interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 18th day of December 2024.



Monique Vouthouris, CCR, RPR, CRR
Notary Public of the State of New Jersey
My commission expires: April 8, 2029