1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 ----------x

4 MERCK SHARP & DOHME LLC,

5 Petitioner,

6 -against-

7 THE JOHNS HOPKINS UNIVERSITY,

8 Patent Owner.

9 ----------x

10

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

12

13 STENOGRAPHIC DEPOSITION OF:
ALFRED I. NEUGUT, M.D., Ph.D., MPH

14 Thursday, August 8, 2024
7:31 a.m. - 3:31 p.m. | Pages 1 - 218

15 ***HYBRID DEPOSITION***

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

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JHU 2163
Merck Sharp v. Johns Hopkins
IPR2024-00647

STENOGRAPHIC DEPOSITION on behalf of Patent Owner of ALFRED I. NEUGUT, M.D., Ph.D., MPH, taken in the above-entitled matter before RICHARD GERMOSEN, Fellow of the Academy of Professional Reporters, Certified Court Reporter, (License No. 30XI00184700), Certified Realtime Court Reporter-NJ, (License No. 30XR00016800), California Certified Shorthand Reporter, (License No. 14391), NCRA/NY/CA Certified Realtime Reporter, NCRA Registered Diplomate Reporter, New York Association Certified Reporter, NCRA Realtime Systems Administrator, taken at the offices of PAUL HASTINGS LLP, MetLife Building, 200 Park Avenue, New York, New York 10166, on Thursday, August 8, 2024, commencing at 7:31 a.m.

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I N D E X

WITNESS	EXAMINATION
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BY ATTORNEY McCORMICK	8

E X H I B I T S

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Exhibit 2058	article in Frontiers in Oncology entitled Prognostic and therapeutic impact of the KRAS G12C mutation in colorectal cancer	44
Exhibit 2059	article in Journal of Oncology entitled Cost-effectiveness analysis in biomarker-guided treatment for metastatic gastric cancer in the second-line setting	50
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**original exhibits returned with original transcript by SULLIVAN GROUP to FISH & RICHARDSON PC
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DIRECTION TO WITNESS NOT TO ANSWER

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P R O C E E D I N G S

7:31 a.m.

CERTIFIED STENOGRAPHER: On the stenographic record at 7:31 a.m.

Good morning. My name is Rich Germosen. I am a certified stenographic reporter. My license is available for inspection.

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

A L F R E D I. N E U G U T, M.D., Ph.D., MPH, (witness produced a New Jersey driver's license), 585 West Englewood Avenue, Teaneck, New Jersey 07666, having been first duly sworn or affirmed, was examined and testified as follows:

EXAMINATION BY ATTORNEY McCORMICK:

BY ATTORNEY McCORMICK:

Q. Good morning, Dr. Neugut.

My name is Madelyn McCormick, and I represent patent owner Johns Hopkins in this proceeding, and I have some questions for you

today, okay?
A. Yes.
Q. Before we start, I'm going to go over the ground rules for this deposition.
You understand that you are under oath; correct?
A. Yes.
Q. You understand that means you have to tell the truth, the whole truth, and nothing but the truth; correct?
A. Sure.
Q. And you'll do that today; correct?
A. Yes.
Q. You also understand that the testimony you give today is just as important as if you were in a courtroom in front of a judge; correct?
A. Yes.
Q. So you understand that you must give truthful, complete, and accurate testimony today; correct?
A. Yes.
Q. And you'll do that today; correct?
ATTORNEY RATLIFF: I object to the form of the question.

Q. You can answer it, Dr. Neugut.
A. Yes.
Q. If you don't understand my question, please let me know, okay?
A. Yes.
Q. So if you answer a question, it's fair for me to assume that you understood the question; correct?
A. Yes.
Q. If you ever want to take back, change, or modify an answer that you gave today, please let me know, okay?
A. Yes.
Q. We'll take a break about every hour, okay?
A. Okay.
Q. If you ever feel like you need to take a break sooner, please let me know and I'll let you take that break, okay?
A. Thank you.
Q. Is there any reason, medical or otherwise, why you cannot give truthful, complete, and accurate testimony today?
A. No.
Q. You requested that we start this

deposition early today; correct?
A. Yes.
Q. Why is that?
A. So I can get out early. No other reason than that. I thought it was going to run late.
Also, I don't want -- I won't easily be available for another day, and if you wanted to run over, it would be somewhat difficult. I thought it would be difficult to run to another day. Mr. Ratliff replied to me that it was a possibility it might run to another day. I don't know if you had more questions or that was a possibility. The truth is I could do another day, but it would be difficult for me, and I didn't want -- I wanted to minimize the possibility that we would need an alternative day or a second day.
Q. Great. I appreciate that.
Just so you know, I hope to finish today, so we'll do our best to do that.
A. That's fine.
Q. Did you also request not to be video recorded today?
A. No.

Q. So just so we can establish some common terminology today, if I use the term "MSI," will you understand that I'm referring to microsatellite instability?

A. Yes.

Q. What is microsatellite instability?

A. Microsatellite instability is a marker that is present on tumors which reflects an abnormality which stems from what's called a mismatch repair and --

(Clarification requested by the stenographer.)

A. Which stems from mismatch repair and is present on a fraction of tumors.

Q. If I use the term "DMMR," will you understand that I'm referring to mismatch repair deficient?

A. Yes.

Q. And if I use the term "CRC," will you understand I'm referring to colorectal cancer?

A. Yes.

Q. And can we also agree for efficiency sake that if I say MSI high, it will encompass DMMR as well?

A. I will understand that the two terms are for practical purposes synonymous.

Q. And if you ever want to distinguish between the two, please let me know in my question.

A. I would use the terms interchangeably as well.

Q. Great.

Dr. Neugut, you're a clinical oncologist; correct?

A. Yes.

Q. You're an epidemiologist as well?

A. Yes.

Q. You treat cancer patients; correct?

A. Yes.

Q. Do you treat CRC patients?

A. Yes.

Q. About how much of your practice would you say is treating CRC patients versus other types of cancer patients?

A. 80 to 90 percent.

Q. So most of the patients that you're treating are CRC patients?

A. Yes.

Q. Do you treat patients with

metastatic CRC?
A. Yes.
Q. What does metastatic mean?
A. Metastatic means that the tumor has spread from beyond the original site of origin from the colon or the rectum and has spread to distant organs, the liver, the lung, or other sites in the body.
Q. And metastatic disease is something different than measurable disease; is that right?
A. Yes, they're different terms, yes.
Q. What is the difference between the two terms "metastatic disease" and "measurable disease"?
A. Well, the truth, they're -- it's total different terms. I mean, measurable means it's a term that's used -- metastatic I already defined, and measurable means -- is a term that's used for assessing the progress of treatment for patients. If you want to know how a patient is responding to therapy, then we utilize -- we measure the tumors to see if they've shrunk or if they've gotten larger, and to do that we literally put calipers on

them or do something of similar sorts to see if they've gotten bigger or smaller.

Not every tumor is measurable. We have to have sort of a clear tumor, like a lump, or on a radiograph, a tumor which is circular, or something like that where it's clearly outlined on the radiograph so that you can measure it. Some forms of tumor are not easily measurable. So although it's measurable, although they may be metastatic disease, they would not necessarily be measurable, but that's what measurable means.

In the context of -- so in day-to-day clinical oncology, we utilize measurable disease in that fashion. It's almost always a requirement in trials, because in trials you want to assess progress of treatment. It's almost always a criterion in solid -- we're talking about solid tumor oncology to determine how a patient is responding to treatment.

Q. So is it true that measurable cancer refers to a cancer that has a minimum size?

ATTORNEY RATLIFF: I object to the form

of the question.

A. I don't know what minimum size means.

Q. So there has to be some amount of the cancer on the radiograph, for instance, that you can measure in order for it to be considered measurable disease; correct?

A. Yes, there has to be -- it has to be visible, and as I said, it has to be measurable. You can measure every -- not every tumor is measurable.

Q. What do you mean by that? Can you give me an example?

A. So if a patient has what's called a pleural effusion, a pleural effusion is a fluid around the lung. So that's metastatic -- I'm talking about pleural, a pleural effusion stemming from the tumor, so that is -- that may be -- that's metastatic disease. It's metastasized from the tumor, and it would make a patient stage four or metastatic disease, but you can't measure fluid like that. You could not put calipers on it and say how big it is and things like that or measure its progression easily in a

quantitative way.

So that would not -- if that was the only site of the disease a patient had, it would not be possible to make a clear-cut quantitative assessment to progress or regression using that. You could say something, I don't know, estimated, or you could say, Well, it got a little better. It got a little worse, but you could not make a measurable assessment exactly how much bigger or how much smaller it got. So that would be an example of nonmeasurable metastatic disease.

Q. Great. Thank you.

Dr. Neugut, have you ever conducted a clinical trial for a cancer therapy?

A. I have participated in innumerable clinical trials, either as putting patients into them or as a co-investigator, but I can only think of one or two where I've actually been one of the PIs. It's not my primary area of interest as a researcher. So I don't normally -- I don't normally conduct clinical trials as my main activity.

Q. What is your primary area of

interest for research?

A. I do two things. I do -- I'm a cancer epidemiologist. So I do studies that focus on cancer etiology and cancer prevention, why you get cancer, causes of cancer, and things like that, and then stemming from that, how to prevent those causes, and how to reduce cancer occurrence related to that. So that has been, from the start of my career, the main focus of my research career.

For the last 20 years, I would say I also have done what's called health outcomes research. So health outcomes research is the application of epidemiologic methodology to clinical questions. So it uses the same statistical and study design methods that we use in epidemiology, but rather than addressing ideologic questions, like is used in classical epidemiology, it addresses questions in clinical medicine.

So, for example, what I've studied is quality of care in oncology. If someone is supposed to get, for example, in stage three colon cancer adjuvant therapy for their colon

1 cancer. Do people with stage three colon
2 cancer get the treatment they're supposed to
3 get. If they don't get it, why don't they get
4 it? Who doesn't get it? Is it because of
5 socioeconomic reasons, age, comorbidities,
6 race and ethnicity, where they live, access to
7 care, issues like those kind of questions,
8 again, addressing quality of care. I've been
9 very involved in questions like medication
10 adherence, who doesn't take their pills, you'd
11 be astounded at how big a problem medication
12 adherence is in general in medicine and in
13 oncology as well, and questions of that sort.
14 So that has been a major issue for
15 me or major area that I've addressed in
16 oncology. And, by the way, even with regard
17 to drugs, like pembrolizumab and
18 immunotherapy, I just had an editorial in JCO
19 which looked at the use of immunotherapy and
20 patients near the end of life and its use or
21 misuse and questions like that. So again,
22 questions addressing like that in quality of
23 care in oncology in particular. And more
24 recently, again, if you're asking what I do,
25 which I'm happy to talk about, I've been

mainly studying also cancer in Africa who gets treated, how care is given in cancer in Sub-Saharan Africa, particularly with regard to HIV and HIV positive versus HIV negative patients, how that affects care and questions like that, so I've been doing that for about 15 years.

Q. It sounds like you do a lot of important work, Dr. Neugut. Thank you for that.

So I just want to make sure that I understand.

A. Uh-huh.

Q. So one of your primary areas of research interest is cancer epidemiology, so prevention of cancer. Did I get that right?

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

A. Yes.

Q. And then another area of your primary interests for research is researching questions in clinical medicine regarding quality of care; is that right?

A. Yes.

Q. And then another more recent,

although you've been doing it for 15 years, primary area of research interest is studying cancer in Africa; correct?

A. Yes.

Q. Any other primary research interests?

A. If you look back over my 40-year career, the answer is I did have a lot of interest in what is called multiple primary cancers, that is the occurrence of more than one cancer in individuals, which is a major occurrence, probably 15 percent of patients get more than one cancer or something like that. So I've studied that extensively as well. I think I'd be considered a major expert on that subject. I actually have a book on it, it's on Amazon if you want to buy a copy. So I would consider that another major area of interest.

I've written over 800 papers, so there is a lot sprinkled in there, where I've had about 80 or 100 postdocs or graduate students. So I've worked with them on a whole range of topics. So again, I've been involved in research on any number of things, which has

really been me collaborating with the fellows and postdocs. So I have publications on any number of other topics, which are different from the three or four areas I've just described as my -- I'll call my personal areas of research interest.

Q. You said that you were a PI on one or two clinical studies?

A. Uh-huh.

Q. Is that right?

A. Yes.

Q. And what do you mean by PI?

A. Principal investigator.

Q. And what's the role of a principal investigator on a clinical study?

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

A. It's a person who is in charge of it.

Q. Does the principal investigator design the study?

A. Again, most studies that I participate in are multiperson things, and so it's hard to say sometimes who does what.

So these are group efforts, and so

who exactly to say design is a loaded word. Let's say the person who may have had the idea, the person who is the senior person and is over the junior person who had the idea. It's hard to say sometimes who is the -- who is responsible and who is -- if you talk about a PI and who is really doing what, it's sometimes a little blurry or ambiguous, but the PI, the principal investigator, is generally the person who is responsible for -- overall for finances, for submitting the grant for the contract or -- which is ultimately generated for the grant, for the publications that stem from it, for telling everybody what to do and all of that. Their name is the one that signs the proposal or the contract or the grant or whatever. Again, exactly who really does what? That's -- as I say, that may be a little -- a little more difficult to discern, but the PI is the one whose name is at the bottom line overall and who is responsible.

Q. Those one or two clinical studies where you had the in-charge role as PI, at a high level, what were those studies about?

A. I did a randomized trial. I told

you one of my interests was medication adherence. So I did a randomized trial at SWOG. SWOG is -- many trials in oncology are done in what are called cooperative groups. I don't know if you're familiar with that or if you need me to explain? Do you need me to explain what a cooperative group is?

Q. No, that's fine. And I'm really just asking like generally --

A. Okay.

Q. -- what those clinical studies --

A. Yeah.

Q. -- you're studying?

A. So it was a trial to see if sending text messages to patients who were taking an oral medication, sending them text messages would enhance their adherence to the drug. Tamoxifen, women take tamoxifen for breast cancer for five years. It turns out more than 50 percent of women stopped taking the drug along the way, which is real negative. It's a very efficacious drug, so we did a randomized trial to see if by sending them text messages two or three times a week, that would enhance the adherence of their compliance with taking

the medication.

They got a text message: Tamoxifen is good for you. Keep taking it. Good girl -- well, not girl. Good woman or whatever. You know, and do that for -- and then measuring their adherence to the drug to see if it would help, and while the other was a randomized trial, the second half of the group -- second arm didn't get text messages, and then after three years to see if there was enhanced use of the tamoxifen in the text message group.

Q. And did you know the outcome of that trial before you got the results?

A. How would I know the outcome of the trial before I got the results?

Q. So fair to say you didn't know the outcome until you got the results; right?

A. Right.

Q. And then what was the other trial that you were a PI for, just again at a high level?

A. Oh. I'm not remembering it as I sit here.

Q. Was it epidemiology-related?

A. Also prevention trial. So again, we do prevention trials, but I'm not remembering exactly what it was at the time.

Q. That's fine.

A. It's quite awhile ago.

Q. Great.

So have you ever designed a clinical trial for testing a cancer therapy?

A. I haven't been the PI predominant. I've helped some of my fellows or students with writing the protocols for it, but I haven't personally been the PI at such a trial.

Q. So have you developed a method of treatment for use in a clinical trial testing a cancer therapy?

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

A. I don't know what the question means.

Q. Fair enough.

I'm trying to ask if you have come up with a novel method of treating cancer before?

ATTORNEY RATLIFF: If that's the

question, I object to the form of the question.

A. I can't recall ever doing that, no.

Q. In your experience, you're aware that clinical -- cancer trials can fail; correct?

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

A. I'm sorry, I'm aware that what?

Q. You're aware that clinical cancer trials can fail?

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

A. What do you mean by "fail"?

Q. So clinical cancer trials cannot meet primary endpoints; correct?

A. Again, I'm not sure we're using terminology in the same way. I mean, to me, a trial is supposed to answer a question does a drug reduce mortality. So if a trial is conducted and the drug does not reduce mortality, to me, that was a successful trial.

I don't know if you call that a failure or if you don't call that a failure. I call that a good trial because it answered

the question that the trial was designed to answer. So I don't know if that answers your question.

Q. So what do you call it, just because you have the terminology obviously that I do not, if a trial is conducted and the drug does not reduce mortality, presumably that didn't meet the primary endpoint if that was the point of the study; correct?

ATTORNEY RATLIFF: I object to the form of those questions.

A. Well, again, so if you ask me -- when you say a drug -- a trial failed, that means to me that you tried to do a trial and you were unsuccessful in being able to conduct a trial.

So let's say when you do a trial, you have a recruitment goal based on statistical power and issues of that sort. So let's say you wanted to recruit 100 patients and randomize 50 to an arm, but for whatever reason you couldn't find 100 patients who met eligibility criteria and you only found 60, so you had to discontinue the trial, you know, halfway through or whatever it was, to me,

that was a failed trial, the trial failed. So you couldn't finish it. So that to me is a failed trial.

So when you ask the question, that's what I saw as failure, but to me, when you conduct a trial, you ask a question, Does a drug improve mortality or does it not improve mortality, in which you then recruit 100 patients, you randomize 50 to arm A and 50 to placebo, and then you conduct a trial, and at the end you get a clear-cut answer, Yes, it does improve mortality, or no, it does not improve mortality. You've got an answer, a clear answer. That was a great trial, and if the answer was no, okay, tough, but -- and maybe the drug company is not happy because they wanted it to be positive, but at least they got a good answer and now they can go on and, you know, take the drug to some other tumor or do something else with the drug or not waste more money on developing the drug further, but they got a clear answer and they should be pleased -- in my mind, they should be pleased with the trial and happy with it.

What's an unsuccessful trial is

either that you couldn't finish the trial or you get an ambiguous answer where it's sort of, Well, it got a trend to a positive answer. That sometimes occurs. It was a .08, they'll say, or this or that, and at the end, they'll argue over whether it was positive or not. It was positive in a subgroup or, you know, things like that. So then you end up not knowing what the result was, and that's -- that's to me, an unsuccessful trial and a trial that gives difficulty to the investigators and to the -- again, I'll say the drug company, if we're talking about drug company trials.

So that's when you do have a problem, because then you don't know -- you don't know what to do. Should we dump the drug or should you exalt the drug. You don't know what to do after that, and that's the problem in a trial, not -- a good no is a good no. That's great, you know.

Q. So I want to ask you about these good no trials.

A. Uh-huh.

Q. How would you talk about those?

Like is there a phrase we can use for that kind of trial?

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

A. Negative.

Q. Negative trial?

A. Not negative trial. Well, a trial that got a negative result. I mean, you know, trials either get a positive result or a negative result. If the experimental drug, the experimental arm, it could be a drug, it could be a combination regimen, or whatever it is, if the intervention, you know, the experimental intervention, it can either be positive in terms of say in comparison to the comparison arm, if it improved the outcome, whatever the outcome was. So that's a positive result.

If it was negative, if it was negative, now you can also get a null result. So that -- so here actually there is ambiguity in the way -- so we're talking about ambiguity in the way people talk. People don't talk correctly. I'm talking about my colleagues. Everyone uses terms incorrectly, and I'm

talking about other oncologists.

So let us say arm A versus arm B, the two arms have the same outcome in terms of survival. So they'll call that a negative study, and that has a negative result. That's the incorrect term. It's not negative. It's null. Again, speaking as an epidemiologist and study design expert, I'll give myself that designation, the truth is, but the correct term is a null result, N-U-L-L.

A negative, a negative result really means that arm B, the control arm, was better than arm A, than the intervention arm, because you can just as well -- if you're comparing treatment A to treatment B, you can just as well have treatment B be better than arm A, and what are you going to call that? The answer is that's a negative result, that that's negative. That treatment B beat, if you want to use that word, that treatment B was better than arm A. That's a negative result.

So when the two survival curves overlap each other, that's a null result. The truth is that in real life, in day-to-day

practice, at meetings, or whatever, if arm A and arm B overlie each other and are the same, everyone calls that negative in day-to-day terminology or nomenclature, but technically they're incorrect. It should be -- the correct term should be null, and it's negative when the other arm is better than -- you know, improves survival compared to arm A, which can happen, which can happen.

Q. Okay. Great.

So I want to make sure that we use the correct terminology today. So a trial with a negative result means that the control arm did -- had better results than the intervention arm?

ATTORNEY RATLIFF: Let the counsel finish her question.

If you finished your question, I object to the form of the question.

A. So a negative result means that, yes, that the control arm improves survival, let's say we're talking about survival as the outcome, relative to the experimental one.

Q. And a null result from a clinical trial is that the intervention arm and the

control arms perform the same?

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

A. Yes.

Q. So clinical trials can have negative results; correct?

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

A. Yes.

Q. And clinical trials in oncology can have null results as well; right?

A. Yes. Again, I just want to make clear that in real life, and I don't even know how it's written in the actual articles, I mean, if you read the articles, you know, the descriptions of the trials in journals, I don't know if you see the word "null" utilized. They will refer to them as negative results if the two arms overlap each other and are similar.

Again, maybe I'm being overly technical, you know, as an epidemiologist and quasi statistician, but I'm simply saying that that's -- those are the correct ways to address it, because otherwise, what would a

clinical trialist say about if its control arm beat out his experimental arm? How would he refer to that? And the answer is that's so far from his -- that's so far from his thoughts, he doesn't anticipate it, so far out of his way of thinking that he doesn't think about it. So he doesn't care about it.

Q. In your experience, do clinical trials in oncology get negative results often?

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

A. Not often, but occasionally, and again, we would have to broaden our -- broaden our universe of what we call "clinical trials in oncology."

If you refer solely to drug trials, then the answer is not that often, but if you expand the definition, and I would, to, for example, supportive care trials, let's say of antiemetics or pain drugs or things like that as opposed to purely therapeutic drugs, then the answer is yes, then you start to see an occasional comparison arm that goes the other way.

Don't forget, there was controversy

over the use of the p-value -- of a two-sided p-value, again, I don't know how much statistics you know -- are you familiar with statistics?

Q. Enough to know what a p-value is.

A. Well -- so there are p-values that are two-sided as opposed to one-sided. Are you familiar with that concept?

Q. (Indicating.)

A. Yeah. So not infrequently in the past investigators tried -- did use and wanted to use one-sided p-values, because by using one-sided p-values they would get away with using fewer subjects in their trials, so you didn't have to utilize as many patients in a trial.

The problem is if you use a one-sided p-value, it eliminates the ability to see if the comparison arm is better than the experimental arm. So they would miss occasionally seeing the ability of the comparison arm to be better than the experimental arm, and ultimately, the journal editors and the powers that be decided that this was not -- this was not a good way to do

trials.

So now, no one will allow a trial to be conducted without having a two-sided p-value, and if you have to then recruit more subjects in order to fulfill the necessity of having a two-sided p-value, tough on you, and that's precisely because they wanted to allow for the possibility that the comparison arm, the control arm, would be better than the experimental arm.

So that's why we have always now two-sided p-values. I mean, we'll never see a paper anymore, a study, or a trial without a two-sided p-value exactly for that reason.

Q. You had mentioned experimental arm and I wanted to ask you about that.

The clinical trials are experiments; right?

A. Yes.

Q. Clinical trials are testing a hypothesis about what might work?

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

A. They should be. I mean, so they don't all, but it depends on what kind of a

clinical trial you have.

Q. So if you can help me just at a very high level, what is a Phase I clinical trial?

A. So a Phase I clinical trial does not have a hypothesis. So it's not truly an experiment, at least in the way I would define an experiment, because it doesn't have an a priori hypothesis.

The goal of a Phase I clinical trial is not to tell us if the drug that's being tested works, if it improves some outcome for a disease, for some cancer.

A Phase I clinical trial is to test -- to see -- so it's for a drug that's not been used previously in humans. It's been tested in animals or primates or whatever, and now it's ready for humans, and so you take the drug and you give it to humans for the first time. The scientists at the drug company, at Merck or wherever else, and you give it -- and they've -- based on their testing, have come up with a dose and a method of administration for the drug, and now they start off at a dose that they think will be safe, and they usually

start off lower than what they think will be the ultimate successful dose, because again, they don't want to knock anyone off, and they started this lower dose. They give it to a few patients and see how it goes and see what adverse effects will occur.

So the purpose of a Phase I trial is dose testing and the determination of, I'll call them, common adverse effects, because again, you're not giving it to a lot of patients. So you want to see what side effects are going to occur.

If you give it to, let's say, six, seven, eight patients at a certain dose level and nothing terrible happens, you know, you don't get major toxicity, then they will move on to a next prespecified dose level and give it to another six, seven, eight patients, and repeat again, see how they tolerate the drug and see if any major side effects occur.

Now, occasionally, there will be a major side effect that no one had anticipated, or something bad will happen and the drug will disappear from the market or something, you know, bad will happen, but more commonly what

will happen is nothing bad will happen and they'll move on to a third or fourth or fifth dose level, and ultimately, they'll reach a prespecified end, because usually it's from end at which they'll stop, they won't go higher than a certain level, and hopefully there won't have been some terrible side effect along the way which will have made them stop along the way, and based on the Phase I trial, they'll decide on what is the best dose at which future testing will occur.

Because they're not testing for effect, for efficacy, a Phase I trial will usually use a mix of tumor sites. So it's not going to be everybody with breast cancer or everybody with colon cancer. It will have a few breast cancer patients, a few colon cancer patients, few lung cancer patients all mixed together. So it's not homogeneous in terms of tumor sites.

If you get some responses, any responses in the Phase I trial, then that is -- I would say everyone like raises a glass of champagne, because that is really -- a really good sign. If you get one or two or

three responses in a Phase I trial, because that wasn't the goal, so if you do get a few responses there, that is considered really outstanding for the drug, and it's -- it -- it presages that it will be an active drug going forward, and whatever tumors it was, that might be the first tumors, then go on to test in a Phase II trial.

Q. So then what is a Phase II trial?

A. So a Phase II trial, now coming out of the Phase I trial, you have a dose or a method of administration that you have now defined based on the Phase I trial, and then the Phase II trial you're looking for efficacy. So you'll give it to some number of subjects with a specific cancer, breast, colon, lung, whatever, so you may have multiple Phase II trials, one for each -- one for each cancer -- one for each cancer you want to try, and you'll give the drug to them. Now, you have to have measurable disease so that you can determine if the tumor responds, and you give it to 25, 30, whatever it is, patients and then you see what happens.

And again, I would say that, again,

if you get one or two responses in 25 or 30 patients with metastatic, I don't know, colon cancer or breast cancer, whatever it might be, in a Phase II trial, again the drug is doing pretty -- that's pretty good for a Phase II trial, and you don't get that many positives.

I mean, speaking overall for Phase II trials, you know, people think that they do so well, but the truth is the overall response rate in Phase II trials is, I don't know, only a few percent. So they don't do that well, but who knows. You never know. You never know who is going to be the next big winner, right?

Q. Do you know what a basket clinical trial is?

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

A. A basket clinical trial is where you treat subjects. It's sort of like, as I said, a Phase II trial, as I just said, was where you treat a homogeneous group of sites. In a basket trial, you sort of -- like you don't limit the Phase II trial to a specific site.

Q. And are you familiar with all-comers clinical trials?

A. I saw this term in Dr. Lonberg's whatever it is, affidavit or whatever it's called. I'm not sure it's actually a term that's like technically used, but, I mean, I can understand what it is. I assume it's a trial where everyone at a given -- at a participating institution is invited to participate in a trial.

I mean, by that definition, I'd say every trial is an all-comers trial to be honest, so I -- I -- it doesn't have that much meaning to me.

Q. How about biomarker stratified clinical trial designs? Does that have meaning for you?

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

A. Again, it has the meaning that it says. I mean, it's a straightforward term. I mean, are you -- subset the participants on the basis of a biomarker as to whether they're positive or negative or whatever on the basis of a biomarker.

Q. Dr. Neugut, are you an inventor on any patent?
A. No.
Q. You haven't filed a patent application?
A. No.
Q. I think you said you'd authored over 800 articles; is that right?
A. Yes.
Q. Let's look at one of them.
ATTORNEY McCORMICK: We'll mark this as Exhibit 2058.
(Whereupon, article in Frontiers in Oncology entitled Prognostic and therapeutic impact of the KRAS G12C mutation in colorectal cancer, is received and marked as Exhibit 2058 for Identification.)
CERTIFIED STENOGRAPHER: Number 2058.
ATTORNEY RATLIFF: And I'll just object to Exhibit 2058 for the purposes of authentication, foundation, and hearsay.
BY ATTORNEY McCORMICK:
Q. Dr. Neugut, do you have Exhibit 2058, which is an article titled: Prognostic and therapeutic impact of KRAS G12C mutation

in colorectal cancer, in front of you?
ATTORNEY RATLIFF: You read that incorrectly. I object to the form of the question.
A. Yes.
ATTORNEY McCORMICK: I'm sorry, counsel, how did I read that incorrectly?
ATTORNEY RATLIFF: You did not read all the words that are in the title. You skipped out words in the title and was representing that that was the article and that's incorrect.
Q. Dr. Neugut, is Exhibit 2058 titled: Prognostic and Therapeutic Impact of the KRAS G12C Mutation in Colorectal Cancer?
A. I have it.
Q. And the title I just read is the title of the article number Exhibit 2058 that you have in your hand?
A. Yes.
Q. Do you recognize Exhibit 2058?
A. Yes.
Q. And how do you recognize it?
A. What does that mean? What does that mean?

Q. Are you an author of this article?
A. Yes.
Q. Do you recognize this article?
A. Yes.
Q. What was your contribution to this article, Exhibit 2058?
A. The Journal Frontiers in Oncology where this appeared was doing a special issue on colon cancer and that was edited by Paul Ruff, a colleague of mine, or you can see on the title page his name, and he invited me to submit a paper on biomarker -- on a biomarker in colon cancer.
So actually I was the invitee for this paper. So I thought about it and I knew of work that my colleague, Dr. Herzberg, who is another one of the authors, was doing on the KRAS G12C mutation, and so I approached him about doing the review article on that subject.
Q. And this article published in September 15, 2023; correct?
A. Yes.
Q. And this article discusses MSI and DMMR; right?

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

A. I don't know. As I'm sitting here, I don't have a recollection.

Q. Okay. If I can point you to page three of Exhibit 2058, the second column under the title: Genetic and Molecular Profile, and the second paragraph down.

Do you see that?

A. Yes.

Q. And do you see there this article that you authored, Exhibit 2058, mentions MSI pathway?

A. Yes.

Q. And this article that you authored, Exhibit 2058, mentions DMMR; right?

A. Yes.

Q. Have you written any other articles that mention MSI or DMMR?

A. I'm sure.

Q. If we have your CV with your articles in front of you, could you identify them?

A. Probably, yes. I mean, it might take me five minutes to identify them, but

yes, I could.
Q. Okay. You and your coauthors sought to provide accurate information in this article; right?
ATTORNEY RATLIFF: I object to the form of the question.
A. I object to the form of the question also. I don't even understand it. You mean did we put in inaccurate information?
Q. I'm not trying to ask you stupid questions. Lawyers sometimes have to confirm these sorts of things.
So is it fair if I ask you again?
A. Yes, we did provide accurate information.
Q. So that same paragraph that I just pointed you to on page three of Exhibit 2053 --
A. Uh-huh.
Q. -- second column, second paragraph, you state in your article: MSI is caused by a deficiency of mismatch repair, DMMR, and is found in approximately 10 to 15 percent of CRC; right?
A. Yes.

Q. And is that still your view today?
A. Yes.
ATTORNEY RATLIFF: I --
THE WITNESS: I'm sorry.
ATTORNEY RATLIFF: It's all right. You already responded.
BY ATTORNEY McCORMICK:
Q. You can set that article aside, Dr. Neugut.
ATTORNEY RATLIFF: Counsel, since you seem to be switching to another exhibit and it's been over an hour, let's take a break.
ATTORNEY McCORMICK: Okay. We can take a break, if that's okay with you. Off the record.
CERTIFIED STENOGRAPHER: Off the stenographic record at 8:34 a.m.
(Whereupon, a recess is taken.)
CERTIFIED STENOGRAPHER: Back on the stenographic record at 8:51 a.m.
BY ATTORNEY McCORMICK:
Q. Dr. Neugut, did you talk about the substance of your testimony with counsel during the break?
A. No.

Q. I'm going to hand you an exhibit we'll mark Exhibit 2059.

(Whereupon, article in Journal of Oncology entitled Cost-effectiveness analysis in biomarker-guided treatment for metastatic gastric cancer in the second-line setting, is received and marked as Exhibit 2059 for Identification.)

CERTIFIED STENOGRAPHER: Number 2059.

ATTORNEY McCORMICK: Correct.

ATTORNEY RATLIFF: And I'll just object to Exhibit 2059 for purposes relating to authentication, foundation, and hearsay.

BY ATTORNEY McCORMICK:

Q. Exhibit 2059 is titled: Cost-Effectiveness Analysis of Biomarker Guided Treatment for Metastatic Gastric Cancer in the Second Line Setting.

Do you see that, Dr. Neugut?

A. Yes.

Q. Do you recognize Exhibit 2059?

A. Yes.

Q. Are you an author of the article that is Exhibit 2059?

A. Yes.

Q. And what was your contribution to this article?

A. As I sit here today, I don't have a good recollection of what I did contribute. I'm sure I read it at the time and reviewed it and made corrections on it. I worked with Dr. Hur, the senior author, and with the other authors on the paper, but I don't recall what else. You know, again, we work in groups and this was a gastric cancer GI group and I was one of the participants in it.

Q. And this article published in 2019; is that right?

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

A. It was published in 2020.

Q. Yes. Thank you.

Article that is Exhibit 2059 published in 2020; right?

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

A. Yes, it was published in 2020.

Q. And this article, Exhibit 2059, looks at the cost effectiveness of pembrolizumab?

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

A. Yes.

Q. And if I could direct your attention to the background section on the first page of Exhibit 2059.

A. Where?

Q. The background section on the first page of Exhibit 2059.

A. Okay.

Q. The second sentence on that background section on the first page reads: Pembrolizumab has shown particular efficacy among patients with programmed death ligand-1, PD-L1, expression, and high microsatellite instability, MSI high.

Do you see that?

A. Yes.

Q. What does that mean?

A. It means that pembrolizumab has some particular efficacy among patients with PD-L1 expression and microsatellite instability.

Q. So what do you mean by "particular efficacy"?

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

A. It means that's where it works.

Q. And if I could direct your attention to the same section a few lines down starting with "results," the sentence reads: The most effective strategy was pembrolizumab for MSI-H patients and ramucirumab/paclitaxel for all other patients adding 3.8 months for 2.0 quality adjusted months compared to paclitaxel.

Do you see that?

A. Yes.

Q. And I just want to focus your attention on the most effective strategy was pembrolizumab for MSI-H patients.

Do you see that?

A. Yes.

Q. And what does that mean?

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

A. This was what's called a Markov model, M-A-R-K-O-V, in other words, this is not a study where there was actually patients

or data, but this took publications from the literature or data from the literature and then did statistical analyses to generate comparisons between different approaches to the treatment of gastric cancer, and in doing that what was found was that for patients that were MSI high that giving pembrolizumab was more -- even though it was a much more expensive drug than conventional chemotherapy, it was more cost effective than giving conventional chemotherapy.

Q. And of all the uses that were studied for this publication, Exhibit 2059, of all the uses for pembrolizumab, the most effective was for the treatment of MSI high patients; is that right?

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

A. Yes.

Q. If you could turn to page two of Exhibit 2059, the fourth paragraph down, the first sentence of that fourth paragraph says: The Cancer Genome Atlas Research Network, TCGA, evaluated 295 primary gastric adenocarcinomas for molecular characteristics

and found that 22 percent had high microsatellite instability, MSI-H; is that right?

A. Yes.

Q. What is the Cancer Genome Atlas Research Network?

A. I don't want to guess. As I sit here now, I would be speculating. I think I know what it is, but I don't want to speculate.

Q. Okay. For this article, Exhibit 2059, you relied on information from the Cancer Genome Atlas Research Network; right?

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

A. That is correct.

Q. And in your experience, does the Cancer Genome Atlas Research Network provide accurate information?

A. I believe so, yes, uh-huh.

Q. So 22 percent of gastric cancers have MSI high?

ATTORNEY RATLIFF: Are you asking about today? What time frame are you talking about?

(No response.)

ATTORNEY RATLIFF: If you won't answer my question, then I object to the form of your question.

A. Again, you're talking about one source of information according to them, yes, but that would be one source. There are other studies and other sources. So I don't know how generalizable that figure would be. Even the next sentence says: However, there is variability based on other published estimates, a recent review estimates that 10 to 39 percent of gastroesophageal cancers are MSI high.

Q. Right. I see the rest of the paragraph.

Gastroesophageal cancer is different than a gastric adenocarcinoma; right?

A. Upper GI cancers are frequently lumped together in citing statistics.

Q. I'm sorry, how does that answer my question? Gastroesophageal cancers are different than gastric adenoma carcinomas; right?

ATTORNEY RATLIFF: I object to the form

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

A. I'm saying when the sentence here talks about gastroesophageal, it includes gastric cancers in its statistical statement. They didn't -- the paragraph, the sentence didn't break down esophagus versus gastric, but gave the statistic as this gastric esophageal cancer together, but that's frequently done --

Q. I've gotcha. Thank you.

So the 22 percent of gastric adenocarcinomas with MSI high, those patients respond best to pembrolizumab as compared to other cancer type -- other cancer treatments; correct?

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

A. This paper wasn't evaluating response rates. This paper was assessing cost effectiveness of pembrolizumab.

Q. So just turning back to that first page that we looked at next to "results," when it says: The most effective strategy, should that say the most cost-effective strategy?

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

A. I'm sorry, where were you reading that?

Q. The first page of Exhibit 2059.

A. Yeah.

Q. About five lines up from the bottom of that indented paragraph where it says "results."

A. Yeah. I think they're talking about most cost-effective strategy.

Q. Dr. Neugut, do you currently prescribe pembrolizumab for your MSI high patients?

A. Are you referring to colon cancer?

Q. Yes.

A. Yes, sometimes.

Q. Can you tell me more about when you sometimes prescribe pembrolizumab?

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

A. I usually -- I usually prescribe immunotherapy. Pembrolizumab is one option. Now, there are other options available. So

sometimes I use pembrolizumab. Sometimes I use other immunotherapeutic agents.

Q. What other immunotherapeutic agents would you use for your MSI high colon cancer patients?

A. Ipilimumab.

THE WITNESS: Good luck.

A. And nivolumab. There is also now a new drug, dostarlinab. Under different circumstances, any of those might be a suitable immunotherapeutic agent, but I do like pembro.

Q. Why do you like pembro?

A. It's easy to give and -- and I tend to use it for older or more frail individuals for those who are sicker. It has a good toxicity profile. So I use it quite a bit actually.

Q. So you prescribe ipilimumab for MSI high colon cancer patients?

A. So there is a combination of ipilimumab with nivolumab, a two-drug -- a two-drug immunotherapy combination, which is also recommended basically in the same context for metastatic colorectal cancer.

Q. And you prescribe dostarlinab for MSI high colon cancer patients?
A. Dostarlinab was reported in the 2023 ASCO meeting as being extremely efficacious in the context of localized rectal cancers. So I prescribed it in that context.
Q. So you don't prescribe dostarlinab in the context of MSI high colon cancer patients?
A. No.
Q. I think we've got a double negative there, so I want to make sure I've got that correct.
Do you prescribe dostarlinab in the context of MSI high colon cancer patients?
A. Not for colon cancer.
Q. And when you use pembrolizumab for your MSI high colon cancer patients, did you first know that they have MSI high colon cancer?
ATTORNEY RATLIFF: I object to the form of the question.
A. Sure.
Q. Why do you find that out first?
A. Number one, it would not be

efficacious in the absence of it being MSI high, and number two, insurance wouldn't pay for it.

Q. Dr. Neugut, I see you have documents in front of you. Can you tell me what those are, please?

A. I have my own declaration in this case.

Q. And is there any markings on that declaration that you have in front of you?

A. I don't have markings on anything.

I have the 2015 New England Journal article from first author Le.

I have a paper by de la Chapelle on microsatellite instability in colorectal cancer.

A paper by Steinert. These are included in the exhibits of my declaration.

A paper by Hamid, H-A-M-I-D, also included in the exhibits.

A paper by Champiat, also included.

A paper by Salipante, also included.

A paper by Pernot, also included.

I have the NCCN guidelines from

2014.

I have the 393 patent from -- the '339 patent.

I have the MSI high study record. That's it.

Q. And why do you have those with you?

A. I anticipated that reference would be made to them during today's deposition. If not, then they'll just sit here until I go home.

Q. Okay. If we could look at your declaration, which is Exhibit 1003, and if you want to look at your copy, that's fine.

ATTORNEY McCORMICK: Sorry, counsel, can I get one back of those so I can give it to the court reporter? Thank you.

Q. Dr. Neugut, do you have Exhibit 1003 in front of you?

A. Yes.

Q. And is this your declaration that you submitted in this IPR for the '393 patent?

A. I'm sorry, did you say IPR?

Q. (Indicating.)

A. I don't know what that is.

Q. So Exhibit 1003 was submitted to

the Patent Office in relation to the '393 patent.

Do you understand that?

A. Yes.

Q. And is this Exhibit 1003 that you have in front of you your declaration?

A. Yes.

Q. And if you'd turn to page 88 of Exhibit 1003, is that your signature, Dr. Neugut?

A. Yes.

Q. If I could direct your attention to paragraph 21, which is on page 20 of Exhibit 1003.

A. Paragraph 21?

Q. That's right. Are you there?

A. Yes.

Q. You state in paragraph 21 that you understand that the terms must be interpreted in light of the patent claims, the patent's disclosure referred to as the specification, and the prosecution history, the record of the back-and-forth between the patent applicant and the United States Patent and Trademark Office during the process of obtaining

allowance of the patent's claims; is that right?

A. Yes.

Q. What is the patent specification?

A. I'm not sure.

Q. I appreciate that you're not a patent lawyer, Dr. Neugut.

The patent specification is the disclosure in the '393 patent that you have in front of you, that's Exhibit 1001, and it's everything but the claims.

Do you understand that?

A. It's everything?

Q. But the claims.

A. I -- I -- I would have guessed that, but I don't want to guess.

Q. I appreciate that. Thank you.

In preparing your declaration that's here in Exhibit 1003, did you read the patent specification of the '393 patent?

A. Yes.

Q. The prosecution history which you have in paragraph 21 is the record of the back-and-forth between the patent applicant and the Patent Office.

Do you understand that?
A. Yes.
Q. Did you read the '393 patent prosecution history as part of preparing your declaration?
A. Yes.
Q. What does it mean to you to interpret the terms in light of the patent claims, the patent specification, and the prosecution history?
A. That the terms are utilized in the same way as they're used by the Patent Office and by the litigants in this affair.
Q. So do you agree that patent claims are typically given their ordinary and customary meaning in their technological field?
A. Yes.
Q. And did you review the words of claim one of the '393 patent?
A. Yes.
Q. And did you understand those words?
A. Yes.
Q. Did any of the words of claim one of the '393 patent strike you as ambiguous,

and I see that you're looking at the patent, so we can look at that also.

A. Well, I want to look at it again and see if ambiguous applies to any of the words.

Q. That's great. Thank you.

And I'll hand counsel Exhibit 1001.

A. The answer is no.

Q. So none of the terms in claim one of the '393 patent strike you as ambiguous?

A. Correct.

Q. Did you find anything in the '393 patent specification that redefined any of the terms in claim one?

A. I don't understand the question.

Q. You reviewed -- sorry. You read the '393 patent specification; right?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. Again, the specification is now -- it's the rest of the patent?

Q. That's right.

A. So I don't have a recollection whether -- this was a long time ago, and as I sit here now, I don't have a recollection if

there is anything in the specification then which contradicts or is not consistent with what's written in claim one.

Q. And if you had found something that contradicts or is not consistent with what's written in claim one, you would have put that in your declaration; right?

A. I don't know because I -- I don't know what it is. I don't know what I would have done.

Q. Okay. So I have the same questions related to the prosecution history. Did you find anything in the '393 patent's prosecution history that redefined any of the terms in claim one?

A. I'll give the same answer. I have no recollection.

Q. Did you review the words of claim 14 of the '393 patent?

A. Yes.

Q. Did you understand those words?

A. Yes.

Q. Did any of the words of claim 14 strike you as ambiguous?

A. No.

Q. Did you review the words of the dependent claims of the '393 patent, so those are the claims other than claims one and 14?
A. Yes.
Q. Did you understand the words of the dependent claims?
A. Yes.
Q. Did any of the words of the dependent claims of the '393 patent strike you as ambiguous?
A. No.
Q. In paragraph 21 of your declaration, you state that no reasonable interpretation of the claim terms, however, would alter your conclusions; is that right?
A. Yes.
Q. And did you consider any different interpretations of the claim terms?
A. I did not or I don't have any other alternative terms.
Q. And in your declaration, you did not provide an analysis of the meaning of "in response to" in your declaration; right?
ATTORNEY RATLIFF: I object to the form of the question.

A. You're talking about the first few words in claim one where it says "in response to determining"?

Q. That's right.

A. No, I did not.

ATTORNEY RATLIFF: I'm not sure what the question is, but I'll just object to the form of the question, as well as to the premise of the question.

A. I'll ask for the question again then.

Q. In your declaration, you did not provide any analysis of the meaning of "in response to"; right?

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

A. I understood the words clearly.

Q. So, Dr. Neugut, you're aware that this is a dispute between Merck and Hopkins; correct?

A. Yes.

Q. And are you aware that Hopkins argued that the phrase "in response to" required no further interpretation?

A. As I said? You mean they interpret "in response to" the same way I do?

Q. I'm not sure.

Dr. Neugut, it's just I'm just asking if you're aware if Hopkins argued that "in response to" required no further analysis or interpretation?

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

A. I don't know what Hopkins argues.

Q. Are you aware that in front of the Patent Office, Merck argued that the claim term "in response to" required no further interpretation?

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

A. I -- I wouldn't know.

Q. In your declaration, did you analyze how different interpretations of "in response to" would affect your opinions?

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

A. Never entered my mind that the

phrase "in response to" would have a meaning different than what it says.

Q. Dr. Neugut, are you aware that there is a District Court litigation between Merck and Hopkins related to the '393 patent?

A. I'm aware that there is a district litigation, a District Court litigation in response to a contract between Merck and Hopkins. I don't know how the patent litigation plays into the contract litigation. So if you're asking me if a patent is at play in the litigation, I haven't a clue.

I think as I understand it, that that was a contract litigation, and I don't know the question as to who is the patent holder or whatever is part of that litigation or not. So I don't have any direct understanding of that litigation.

Q. Okay. So if there was any claim construction or claim interpretation that happened as part of the District Court litigation, you wouldn't be aware of it?

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

A. That's correct.

Q. Now, we talked earlier that you treat metastatic CRC patients; right?
A. Yes.
Q. And you treated metastatic CRC patients before 2015; right?
A. Did I treat metastatic colorectal cancer before 2015?
Q. (Indicating.)
A. Yes.
Q. About how many metastatic CRC patients did you see per week in 2015?
A. In 2015? 10 to 12.
Q. Do you see about the same 10 to 12 metastatic CRC patients per week now?
A. Yes.
Q. And in 2015, did you know at the time you were treating those CRC patients that they had MSI high status?
A. Or not.
Q. Or not?
A. Yes.
Q. And how did you know?
A. It was standard practice to do testing on their tumor samples for MSI status.
Q. And why was it standard practice to

do MSI testing on tumor samples?

A. It was a recognized -- excuse me, it was a recognized prognostic marker. So it's helpful in that respect, and it also -- it also predicted response to 5-fluorouracil.

Q. And are there other reasons that you would be testing CRC patients for MSI status in 2015?

A. You're talking now, before it became standard to give immunotherapy?

Q. I am.

ATTORNEY RATLIFF: I'm not sure what the question is, but I object to the form of the question.

A. Well, it was also a genetic marker. So for the 10, 15 percent who turned out to be MSI high, a substantial fraction of them may have had Lynch syndrome, and if they were MSI high, one would have made certain to refer those patients on to the genetic counselors for genetic testing.

Q. If you knew in 2015 that a CRC patient was MSI high, did you have a specific treatment for that patient?

ATTORNEY RATLIFF: I object to the form

of the question.
A. So in the context of metastatic cancer, the answer is no. In the context of localized cancer, it did affect decision-making there, but I don't think it affected a decision-making in metastatic -- well, in metastatic cancer, you could not give 5-fluorouracil alone without oxalitlatin.
Q. Let's just focus on the metastatic CRC patients in 2015.
A. Uh-huh.
Q. If those patients were MSI high, what treatment options did you have for them?
ATTORNEY RATLIFF: I object to the form of the question.
A. They could get FOLFOX, which was the standard chemotherapy regime that we utilized and that we still utilize even now. What the MSI status affected was that if you were MSI high, it had the effect of -- let me see how I can express this. In effect, if you were MSI high, it was as if you were already treated with 5FU, a patient who was MSI high effectively as if they had been treated with

5FU alone, so you could not treat a patient with 5FU alone. 5FU is probably the best signal drug for colon cancer. Occasionally you may want to treat someone with 5FU alone, but if they were MSI high, you could not do that.

So you could only give FOLFOX the regime 5FU with oxaliplatin. So that was the effect of being MSI high would have in the context of colon cancer. That's still true today. That will be still true now. I mean, but that's still true today, although today you would go first to immunotherapy, but after the immunotherapy, when you shift to a conventional chemotherapy, again, you would still have to give FOLFOX as opposed to 5FU alone. You could not give 5FU alone.

Q. And staying with the 2015 time frame, what was the prognosis for MSI high metastatic CRC patients?

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

A. So --

(Cell phone rings.)

A. Somewhat better than the patient

who is MSI negative, because as I would express it, having the biological characteristic of having been treated with 5FU, it's a good thing. So if biologically you've been, in essence, treated with 5FU, you've -- even though you haven't truly been, it's better than not being treated with 5FU. So they did better than the patients who were MSI negative.

So if survival in 2015 on average for all-comers was -- and I'm going to say in the ballpark of approaching three years average survival, so the MSI high patients would have been on the upside of that, above average, and the MSI negative patients would be a little somewhat below that on the downside.

Q. How did you do testing for MSI status in 2015?

A. How did I do it?

Q. (Indicating.)

A. I sent it to the lab and said, Please test this specimen for MSI status. How they did it? I believe it was mostly done by immunohistochemistry, although at some point

it was done more by PCR. I don't -- I couldn't tell you exactly how they did it. I just get back a lab report that gives a result, and I don't really pay attention to how it was done.

It was at our institution, so if the patient was operated on or biopsied at our institution, it was what we call a reflexive test, meaning that every patient with colorectal cancer, whether it's tumor tissue from a colon cancer, is automatically tested for it. If we had a patient from outside who came for a second opinion or came from another hospital and then came to us subsequently, then we had to obtain tissue from the other hospital and test it.

Q. Again, sticking with the 2015 time frame, at that time did you know about pembrolizumab?

A. I'm sure, yes.

Q. How would you have known about it?

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

A. Well, if we're talking mid-2015, I would have known the paper, and I would have

known the presentation at ASCO that was done, but, you know, those things are sort of -- there would have been talks about it. It would have been described on the -- you know, it would have been described on the grapevine. You know, one would have heard these things. I was already -- it would have been well-known.

You know, so what I would have known is that immuno -- I'm sorry, that immunotherapy would have been effective. So it would have been known also for nivolumab and ipilimumab and all the other immunotherapeutic agents.

I will say that I do not off the top of my head remember from 2015 which agents I would have necessarily have paid attention to and at least until the New England Journal paper or until the ASCO presentation.

Q. The New England paper that you're referring to, is that the New England Journal of Medicine article with Dr. Le as the first author?

A. Yes.

Q. And the ASCO presentation you're

referring to, what's that?
A. So that would have come out roughly the same time or a month or two earlier. It was basically a presentation of the same thing given at ASCO.
Q. Were you there for that 2015 as co-presentation?
A. I was at the meeting. If you ask me was I in the room? You know, the meetings are huge. I never remember -- I don't remember as I sit here if I was there. I would bet I was because I don't think I would have missed that, but I can't swear as I sit here that I remember specifically hearing it, but I was at the meeting, so I would have seen the abstract -- you know, the written abstract in the book for sure. That I definitely saw, and I will -- I would bet that I was at the presentation, but I can't swear to it.
Q. And why do you say that you definitely remember seeing the ASCO abstract?
A. Because I always read through all the GI -- the book is huge. There are, I don't know, hundreds or thousands of abstracts, but I go through the book, and I

certainly read all the colon and GI abstracts and look at them. So without doubt I would have seen them.

Q. And when did you first see the 2015 New England Journal of Medicine article?

A. Whenever it was published. I always -- I get the New England Journal of Medicine, so I -- I get the New England Journal of Medicine, so I -- I would not have missed it.

Q. What did you think when you first saw the 2015 New England Journal of Medicine article from Dr. Le?

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

A. In what spirit is the question asked?

Q. I just kind of want to know what your reaction to it was.

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

A. Well, you know, by then it was

already, I'll use the term, anticipated that that was going to be the case, that immunotherapy was going to work for MSI high patients. I was impressed with the -- I mean, if you look at survival curves, it really is a pretty remarkable difference between the MSI positive and MSI negative groups. You don't frequently see in oncology that dramatic a difference.

Q. Did you use pembrolizumab in your practice in 2015?

A. After the paper.

Q. So before the 2015 paper, did you use pembrolizumab in your practice?

A. So as I said, first of all, it wasn't approved, and while it's true that you can use drugs off-label, so it might have been kosher to do that because the drug was approved and on the market for -- again for melanoma, I don't think it would have been paid for by insurance and the drug is a fortune. So it was impossible to use. The answer is no.

Q. And then after the 2015 paper, you used pembrolizumab in your practice; is that

right?
A. I used it as soon -- well, you had to wait -- I don't know when it was FDA approved. So I don't recall when that -- I don't remember offhand when that occurred. You really had to wait, because these drugs are -- like I say, they're a fortune and no patient can get these drugs without insurance support, and that can take -- I don't know, that can take a while. After it was FDA approved, for sure.
Q. So the results from that -- published in that New England Journal of Medicine article from 2015, they changed your standard practice?
A. I'm sorry.
ATTORNEY RATLIFF: I -- hold on. If you're finished with the question, I object to the form of the question, as well as to the premise of the question.
Q. After you saw the 2015 New England Journal of Medicine article and once pembrolizumab was approved for MSI high colorectal cancer patients, you changed your practice for those MSI high cancer patients?

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

A. That is correct.

Q. And why did you do that?

A. I mean, it's clear that -- well, two reasons. One is the obvious efficacy of the drug in that context, and the second is it's actually a much more tolerable regime. Patients are much happier getting an immunotherapeutic agent than a conventional chemotherapy.

Q. So we talked about the standard of care kind of in 2015 for CRC patients with MSI high tumors. How is that different from the standard of care now for CRC MSI high --

ATTORNEY RATLIFF: I object to the --

Q. -- patients?

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

A. Well, now I am a first-line therapy for a metastatic colorectal cancer patient who is MSI high would need to give one of the immunotherapeutic agents. Again, either pembrolizumab or ipilimumab and nivolumab.

Q. We're using the molecule names for the drugs when we say pembro. Do you understand that's also called Keytruda?

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

A. Yes, we see it on commercials.

Q. So in order to give your metastatic CRC patients Keytruda, do you test their tumors to see if they're MSI high first?

A. Yes.

Q. And if the testing determines that that patient has MSI high, you recommend treating them with pembrolizumab?

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

A. I recommend immunotherapy. Whether it's Keytruda or whether it's ipilimumab with nivolumab vary depending on other issues.

ATTORNEY McCORMICK: We've been going for about an hour. Is it all right if we take a break?

THE WITNESS: Fine.

ATTORNEY McCORMICK: Perfect.

We can go off the record.

THE WITNESS: Uh-huh.

CERTIFIED STENOGRAPHER: Off the stenographic record at 9:50 a.m.

(Whereupon, a recess is taken.)

CERTIFIED STENOGRAPHER: Back on the stenographic record at 10:08 a.m.

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, did you discuss the substance of your testimony with counsel during the break?

A. No.

Q. If I can point you to your declaration, Exhibit 1003, at page 39, paragraph 50. Let me know when you're there.

A. Okay.

Q. As part of your opinions in this dispute, you allege that each and every limitation of claims from the '393 patent, which are here on page 39 of your declaration, are found in the MSI study record; is that right?

A. Yes.

(Whereupon, document previously marked Exhibit 1005, is received and marked as Exhibit 1005 for Identification.)

BY ATTORNEY McCORMICK:
Q. And the MSI study record, that's Exhibit 1005; correct?
A. Yes.
Q. Can you have Exhibit 5 in front of you, please? 1005. Sorry.
A. Yes.
Q. Okay. And if we go in your declaration, Exhibit 1003, to paragraph 59 on page 44, can you let me know when you're there?
A. We're now in my declaration?
Q. That's right.
A. Uh-huh. Okay, uh-huh.
Q. And paragraph 59. You're there?
A. Yeah.
Q. Okay. Great.
You state in paragraph 59: The MSI high study record discusses treating a patient with 10 mgs per kg of pembrolizumab every 14 days in response to a patient meeting the eligibility criterion of having MSI high colorectal cancer; is that right?
A. Yes.
Q. And in support for that sentence,

you point to Exhibit 1005, the eligibility criteria and the arms and interventions; is that right?

A. Yes.

Q. I appreciate your hesitation there.

You also point to additional paragraphs in your declaration; correct?

A. Yes.

Q. If we could look at Exhibit 1005, the MSI high study record.

A. Yes.

Q. So Exhibit 1005 is the MSI high study record that you are relying on for the "in response to" determining that colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab; correct?

A. Yes.

Q. And I appreciate that there are other versions of a clinical study record that were published after the clinical study records shown here in Exhibit 1050.

Do you understand that?

A. Yes.

Q. But when I'm referring to the MSI high clinical study record, I'm only talking about the one here in Exhibit 1005.

Do you understand that?

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

A. I understand that.

Q. And Exhibit 1005 here is the only clinical study record that you are relying on in your declaration; correct?

A. Yes.

Q. If you could turn to page two of Exhibit 1005. Looking down almost to the bottom of the page, the submitted date.

Do you see that?

A. Yes.

Q. And the date of this clinical --

A. Sorry.

Q. Are you okay, Dr. Neugut?

A. Yes, yes, I'm sorry.

Q. Can we get you some water?

A. No, I'm fine.

Q. Okay.

A. I'll try not to cough.

Yeah, so you said to look at the

submitted date, yes.

Q. Yes, and you see the date is June 10, 2013; correct?

A. Yes.

Q. So again, I'm just referring to this version of the MSI high clinical study record when talking about the MSI high clinical study record, okay?

A. Yes.

Q. So looking on page four of Exhibit 1003, the arms and intervention section.

Do you see that?

A. Yes.

Q. And where does it say in the arms and intervention section that you are to give pembrolizumab to patients in response to determining the MSI high status?

A. It says to give it for MSI positive colorectal cancer and then to give MK3475 at 10 mgs per kg.

(Clarification requested by the stenographer.)

A. MK3475 at 10 milligrams per kilogram, and then it has MSI negative and to give the same treatment. Likewise under the

inclusion criteria, it also in arm one has patients with MSI positive colorectal cancer, and in arm two patients with MSI negative colorectal cancer. I think a POSA would have understood that the drug was being given in response to the biomarker and to being MSI positive or being MSI negative.

Q. Is it possible that patients were being given pembrolizumab if they had colorectal cancer regardless of knowing their MSI status at the time that they were given the pembrolizumab?

ATTORNEY RATLIFF: I object to the form of that hypothetical.

A. Then if that were the case, there would have been no reason to do the biological testing and to define who was MSI positive and who was MSI negative, and I think logically this would have been, I don't know, to me silly, and I think a POSA would have understood it that way.

The way the study was conducted, that would not have been a logical way to conduct a trial and to say otherwise is, I'll use the word, absurd.

Q. So is it possible that patients could have been enrolled in this study, been given pembrolizumab, and then the doctors would have determined the MSI high status?

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

A. Is it possible?

Q. (Indicating.)

A. I'm sorry, say it again.

Q. Is it possible that patients could have been enrolled in this study without knowing their MSI status, given pembrolizumab, and then after that, determined the MSI status for those patients?

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

A. That's a hypothetical way to have done it, and that would have been an entirely different trial, but that's not the way this trial was conducted. So the answer is no, that is not possible, and if you actually read the trial, that's not how it was done at all. So the answer is no.

Now, someone else could have done a

trial that way if they wished to, but that's not what was done in this particular trial.

Q. So you read how the clinical trial was conducted?

A. Yes.

Q. When did you do that?

A. In 2015 and during the preparation of these reports and proceedings and in preparation for the deposition.

Q. And you know that this clinical trial that's here in Exhibit 1005 was run in the manner you described because you read the clinical protocol?

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

A. I read the actual protocol at one point, and I also read the New England Journal article.

Q. And because you read the New England Journal article, you know that the patients were tested for MSI status first and then given pembrolizumab; is that right?

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

the question.

A. Patients were recruited on the basis of their MSI status and then recruited on the basis of being MSI positive, that's how they created the MSI positive cohort, and then they recruited another cohort of colorectal cancers and tested them for their MSI status, and that's how they created the MSI negative cohort.

Q. And is that recruitment method here in Exhibit 1005?

A. It's -- I think it's clear that that would have been how it would have had to be conducted, because otherwise you would never know who is MSI positive or MSI negative without doing biological testing to determine the MSI status, and again, anyone would have known that or understood that to be the case. It was mandatory.

Q. So regardless of MSI status, all of the patients enrolled in the MSI clinical study that's reflected here in Exhibit 1005 were given the same intervention; correct?

A. That's correct.

Q. So would it make sense that you

could enroll patients with colorectal cancer, give them the drug, and then determine their MSI status and assign them to a different arm?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. Say that again.

Q. So would it make sense because the interventions are the same that you can enroll colorectal cancer patients in the study here reflected in Exhibit 1005, give them the drug, and then determine MSI status to assign them to the different arms?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. You mean determine the MSI status after you've administered the pembrolizumab?

Q. Correct.

A. You could have done that, but that's not what was done and it's not what's implied. So the answer is no.

Q. And why do you say that's not what's implied?

A. Because -- well, theoretically, it is possible, then you would have had to treat hundreds of patients in order to achieve -- in

order to achieve that, and so I guess theoretically, it is possible, but I would say that that would be an incredibly inefficient way to do the study, and it would be -- the rate of MSI in metastatic colorectal patients, the patient population that's being entered in this trial, the rate of MSI positivity in that population is about 4 percent.

You know, while we talked about 10 to 15 percent of MSI in colorectal cancer overall, that isn't true in the metastatic setting. In the metastatic setting, the rate of MSI positivity is 4 percent.

So if you had to find patients who fit the eligibility criteria, metastatic colorectal cancer, who had failed to prior treatments and had measurable disease and you wanted to find enough patients who are going to be MSI positive, at 4 percent, 4 percent, and you wanted to get -- let's say in this case I got 10 patients who were MSI positive, at 4 percent you'd need 400 patients, you'd need to enter 400 to 500 patients, to find them. That would be an incredible -- incredibly inefficient and stupid way to do

the trial. I guess theoretically, if you wanted to, you could do it that way, but I don't think a POSA or the Johns Hopkins group or Merck would have been dumb enough to do that, and they were not.

They did it in a correct way or in a logical way or the efficient way. So you're right. There could be a way to do it where you put your arm around your head and put your left elbow in your right ear, but that would not be the smart way to do this, so that's my answer.

Q. I appreciate that. Thank you.

And the only way you know for sure how the clinical trial was actually performed is because you read the New England Journal of Medicine article discussing it; correct?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. Well, I think the protocol says how it was done, although it doesn't give the exact details as it was actually done in the -- it tells it somewhat differently in the study protocol as I recall and it was a while --

(Clarification requested by the stenographer.)

A. It tells it somewhat differently in the study protocol than it does the actual New England Journal article, but it's effectively the same.

Q. We were talking a little bit ago about the phrase "in response to."

Do you remember that?

A. I remember alluding to it. You were talking about it.

Q. Fair enough.

Do you remember that I was talking about the phrase "in response to"?

A. Yes.

Q. Do you agree that this phrase requires a cause and effect?

A. Requires an exposure and an outcome.

Q. Is that different than a cause and effect?

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

A. You used the word "cause." I used exposure, but okay.

Q. In the inclusion criteria section of Exhibit 1005, is there anything in there about requiring previous treatments?

A. Requiring? I'm sorry?

Q. Previous treatments?

ATTORNEY RATLIFF: Just so I'm following along, what do you mean by "inclusion criteria"?

(No response.)

ATTORNEY RATLIFF: If you don't want to respond to my question, then I object to the form of your question.

Q. Dr. Neugut, on page five of Exhibit 1005, somewhat near the middle it says: Criteria, inclusion criteria.

Do you see that?

A. Yes.

Q. And under that heading there is numbered sentences.

Do you see that?

A. Yes.

Q. And are any of those numbered sentences about requiring previous treatments?

A. No, but I will say that it would have been unethical and virtually impossible

for an experimental study of metastatic colorectal cancer to put a patient on an experimental drug in 2013 or '14 or '15 without having given -- without the patient having received prior chemotherapy and having progressed on it, that would have been unethical and would never have been approved.

This is not a well-written -- I think this is a very poorly written experimental protocol. It leaves out a few things, but that's left -- it should have been written explicitly here.

Q. Why do you think the experimental protocol written here in Exhibit 1005 is poorly written?

A. Well, it leaves out exactly what I just said, what you alluded to, which is that the patients had to have previous treatment and progressed on the previous treatment before being allowed to be put on an experimental drug.

Q. What else does this protocol here in Exhibit 1005 leave out?

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

the question.

A. Well, again, this is -- later on in the claims alludes to giving the pembrolizumab intravenously, and so it has to be given intravenously. That was the only mode of administration that was available, and so that should have been said explicitly in the method of administration. It does say they agree to have a biopsy of their cancer. So that already tells you they have to have a biopsy of their cancer, so that is explicit. Okay.

Q. Anything else left out of Exhibit 1005 besides intravenous administration and requiring previous treatments?

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

A. Most protocols will have a demand that the colorectal cancer be histologically proven. Again, that may sound -- it's like some of the other things. Every POSA will recognize and know that that's a given or an obvious thing, and it would have been done and it had to be done and it would have been done, but it should say it explicitly, protocol

1 should be complete and list every requirement
2 openly, you know, and explicitly. It doesn't
3 say that anywhere here that I see, so it
4 should have said that as well, but it does
5 not.
6 Again, it leaves out certain
7 details. These details would never have been
8 missed in real life. You know, they would not
9 have been violated or missed in the conduct of
10 a real trial, but they should have been
11 explicitly written in the study record.
12 I mean, I can further say again
13 that -- I'm sorry, it's --
14 CERTIFIED STENOGRAPHER: I can't hear
15 you, Doctor.
16 A. It's in the -- there was something
17 else I thought of, but it's in the exclusion
18 criteria.
19 Q. So going back to --
20 A. I'm sorry?
21 Q. Going back to when one would test
22 the MSI status, testing could occur after a
23 patient was enrolled in the study; correct?
24 ATTORNEY RATLIFF: Which study are we
25 talking about?

(No response.)

ATTORNEY RATLIFF: If you don't want to answer my question, I object to the form of your question.

A. I don't understand the question.

Q. So patients would get enrolled into the study that's reflected here in Exhibit 1005; correct?

A. Patient would be enrolled? What patient would be enrolled? I'm sorry. Someone who is at the entry criteria?

Q. Yeah, I'm asking a super basic question.

A patient gets enrolled into the study; correct?

ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise that you're asking a super basic question.

A. Yes.

Q. And is there anything in this study protocol that says a patient's MSI status would need to be determined before enrollment?

A. "Before enrollment" being before they were recruited into the study?

Q. (Indicating.)

A. No.
Q. Were you aware in 2015 that nivolumab had been used to treat CRC patients?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I don't think so.
Q. So is it fair to say that if you weren't aware of nivolumab being used to treat CRC patients, you didn't have an idea of the results?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I don't have a specific recollection of nivolumab and treatment of colon cancer at that time.
Q. I want to talk about ASCO again if that's all right with you.
You refer to ASCO in your declaration; correct?
A. Yes.
Q. And you write that: ASCO is an annual meeting for oncologists which is considered the Super Bowl of the cancer world

and attended by over 40,000 oncologist and other -- others each year; correct?

A. Yes.

Q. You wrote that until 2020, you regularly attended ASCO; right?

A. Well, I stopped going at the time of the pandemic.

Q. And have you restarted going to ASCO?

A. No.

Q. And why is that?

A. Personal reasons.

Q. When did you first go to ASCO?

A. When I was a fellow.

Q. And when was that?

A. I think my first meeting was in 1981.

Q. And why did you go to these meetings?

ATTORNEY RATLIFF: Each and every one? Wait. Hold on. Hold on. I object to the form of the question.

A. It's a place to be. It's where everyone is. First of all, to hear what's new and exciting and also almost more importantly

to hobnob and interact with other oncologists and meet the main players in oncology. So it's the best way to network.

Later when I had fellows of my own, I would go to make sure they would meet to help them network with major players in the field, and then also I present papers. I, as well, lecture there as well. Give talks and present posters and whatever and then also a good place to pick up freebies and stuff like that. So it was a good thing. It's usually in a good place also. So an opportunity to travel a bit.

The last, I don't know, 20 years it's always been in the same -- they stopped moving it, so it's always been in Chicago for the last, I'm going to say, 20 years, so you don't get to see other cities anymore, but it used to be a good opportunity to see other places.

Q. You said you had been invited to give talks at ASCO. Have you ever given a keynote address at ASCO?

A. I don't think so. I mean, I've given certainly oral talks and, you know,

spoken in workshops and things like that, but I don't think I ever gave one of the plenaries or one of the main talks.

Q. In your opinion, is it an honor to be invited to give a keynote address at ASCO?

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

A. I don't know what you mean by a "keynote address." What exactly do you mean? What do you mean by a "keynote address"?

Q. You referred to giving one of the plenaries or one of the main talks.

A. Oh.

ATTORNEY RATLIFF: Wait, if that's a question, which I don't understand what the question is, I object to the form of the question.

ATTORNEY McCORMICK: I wasn't done with the question yet.

Q. So when I'm saying keynote address, I think I mean the same thing as you do about a plenary or one of the main talks.

ATTORNEY RATLIFF: If your question has embedded something about you thinking you know what he means, I object to the form of the

question.
A. Yeah, of course it's an honor to be one of the plenary or main talks.
Q. Do you know why someone would be selected to give one of the plenary or main talks at ASCO?
A. Well, one of the plenary talks would be because of the several thousand papers would be considered one of the main -- one of the most important discoveries of the year among all the abstracts that were submitted.
The other -- I don't know, one of the main -- other main talks would be because someone was being honored. Sometimes there were certain awards that are given out at every meeting, you know, best basic scientist, the best clinical scientist, things like that, so if someone is given one of those awards, then they're invited to give a talk about their work or something like that, so they give those talks.
Q. So you said you recall in 2015, Dr. Le gave one of the main talks at the 2015 ASCO; right?

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

A. I don't -- as I sit here, I don't recall or know, but --

Q. So you have no memory of whether Dr. Le gave one of the main talks at the 2015 ASCO?

A. What does "one of the main talks" mean?

Q. I thought we had established that was one of the more important oral sessions at ASCO.

ATTORNEY RATLIFF: I object to your thought, if that's a question.

A. I didn't say that. If you tell me that it was, I don't have a reason to disbelieve you.

Are you saying it was a plenary talk?

Q. Let me start again.

Do you recall Dr. Le's talk at the 2015 ASCO?

A. I already answered that. I do not recall specifically hearing her talk. It could have -- it probably would have been in

the colon cancer session as an oral talk, and I probably would have gone to the colon cancer early-on talks, and I probably would have heard it, but I don't, as I sit here, have a specific memory of hearing it.

Q. I recall you saying that you get the New England Journal of Medicine; is that right?

A. Yes.

ATTORNEY RATLIFF: You're asking -- it's okay.

Q. Why do you get the New England Journal of Medicine?

A. Well, they send it to me for free, and it is sort of the leading -- the most -- it has I guess the most -- I don't want to say the most important, but certainly the most -- well, I guess the most prominent papers that are published in medicine.

Q. Are you a reviewer for the New England Journal of Medicine?

A. I've reviewed a couple of times for them.

Q. What's your view of the reputation of the New England Journal of Medicine?

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

A. I mean, as I said, it's considered the most prestigious journal.

Q. Have you written any papers that were published in the New England Journal of Medicine?

A. No.

Q. Did you read Dr. Le's New England Journal of Medicine paper before you became involved in this case?

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

A. As I said, I read it in 2015.

Q. Okay. We can go back to your declaration, Exhibit 1003, paragraph 108 on page 61.

Are you there, Dr. Neugut?

A. Yes.

Q. Okay. Your opinion is that the motivation to combine in an obviousness analysis of the MSI high study record, which is Exhibit 1005, and Pernot means a motivation to carry out the clinical trial; is that

right?

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

A. I think Pernot, yeah, gives an increased enthusiasm to conduct the trial.

Q. And if we could look at paragraph 112, which is on page 63, which is still in the same section as paragraph 108.

Do you see that?

A. Yes.

Q. Okay. And your opinion is that a motivation to combine means a motivation to obtain the data from the results of carrying out the MSI high study record; right?

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

A. Yes, I agree.

Q. And a POSA wouldn't know the results from carrying out the protocol disclosed in MSI high study record until they ran the trial; right?

A. They wouldn't know the results, the exact results, until they did the trial, but I

think they would have anticipated that there would have been a positive outcome.

Q. And is it your opinion that if the results naturally flow from the clinical study protocol, the results of that study protocol are disclosed?

A. I don't know what "disclosed" means.

Q. You don't know what discloses means?

A. Disclosed to whom?

Q. To anyone?

A. Could you repeat the question?

Q. So is it your opinion that if the results from the MSI high study record are carried out and those results naturally flow from -- sorry. Let me start again; is that okay with you?

A. (Indicating.)

Q. Is that a yes?

A. Yes.

Q. Is it your opinion that if the results naturally flow from carrying out the MSI high study record protocol, then the results of that study protocol are disclosed

to a POSA?

A. Again, I am unclear as to what you mean by the word "disclosed." You mean that somewhere down the road, that these were done and that it's kept as a secret, but the POSA is told the results in some secret way? Is this a legal term?

Q. I'm using the word "disclosed" in the way that anyone would. Like I mean --

ATTORNEY RATLIFF: Hold on. I would definitely object to that, because how you're using it is not how I would use it, so that's invalid.

What's the question pending?

THE WITNESS: Yeah?

ATTORNEY RATLIFF: Hold on. There is no question pending.

THE WITNESS: Okay.

ATTORNEY McCORMICK: Counsel, you don't need to make a speaking objection.

ATTORNEY RATLIFF: It's not a speaking objection. There is no question pending then --

A. I'm not trying to be difficult. I really don't understand the word.

BY ATTORNEY McCORMICK:

Q. I'm trying to understand in paragraph 112 of your report or your declaration the last sentence: As a result of carrying out the methods in the MSI high study record of treating MSI high colorectal patients with pembrolizumab at the dosage that was applied in the clinical study, the person of ordinary skill would have seen the results that naturally flow from those methods.

Do you see that?

A. Yes.

Q. What do you mean by that?

A. I mean that the -- as I said previously, the POSA would have anticipated that by carrying out the MSI -- the study that's described in the MSI study record, that there would have been a positive outcome from the conduct of the study and would have gotten a positive result as was obtained in the ultimate conduct of the clinical trial.

Again, what the exact number would have been, okay, that, you know, you can't anticipate exactly, but the POSA would have anticipated that there would have been -- that

the drug would have been efficacious in the context of MSI high colorectal cancer and not efficacious in the context of MSI negative colorectal cancer.

Q. I want to focus on the word "seen" that you use here in that last sentence of paragraph 112 of your declaration.

A. Yeah.

Q. Where would the POSA have seen the results that naturally flow from those methods disclosed in the MSI high study record?

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

A. Okay. So perhaps the word "seen" should not be taken literally as seen or have those results to hand, but would have, as I say -- would have anticipated seeing the results might be a better way to phrase my intent.

Q. And your opinion is that based on the MSI high study record, a POSA would have anticipated seeing positive results from carrying out the MSI high study record?

A. Precisely.

Q. A POSA would not have known the

results from carrying out the methods of the MSI high study record until it was carried out; correct?

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

A. A POSA would not have known the exact numbers, of course.

Q. Do you understand that's part of an obviousness analysis, it has to be based on what is in the prior art?

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

A. Yes.

Q. I want to point you to page 62, your footnote seven.

A. 62?

Q. Yeah.

Do you see that?

A. Yeah.

Q. If information is not found in the prior art, that would affect your obviousness analysis; correct?

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

A. I'm sorry, what's your question?

Q. If information is not found in the prior art, that would affect an obviousness analysis; correct?

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

A. To be honest, I don't know the legal implications or how that would affect things.

Q. Fair enough.

I think you have the patent in front of you; is that right? The '393 patent, Exhibit 1001?

A. Yeah.

Q. I just want to focus on the inventor section there.

Do you see that on the first page of Exhibit 1001? It's at the top.

A. On the cover page?

Q. That's right.

A. Yes.

Q. Do you know any of these inventors?

A. When you use the term "know," do you mean do I know them by reputation or do you mean do I play stickball with them?

Q. By reputation is fine, although I

do want to know if you play stickball with any of them?

A. No, I certainly know a few of them by reputation, but I don't -- I don't believe -- I don't know them personally. I probably -- I met a couple of them like in the sense of at a meeting and you shook hands with them at a poster or something like that, but we're not -- we're not friendly. But I don't think I've had dinner with any of them or anything like that.

Q. You said you know a few of them by reputation. Which few?

A. Well, certainly Vogelstein.

Q. And why do you say that?

A. He is, you know, world famous, and Kinzler and Papadopoulos and Pardoll.

Q. Anyone else you know by reputation?

A. No.

Q. And how do you know Dr. Kinzler by reputation?

A. Kinzler I believe was a fellow in Vogelstein's lab, and so Vogelstein is famous for the Vogelgram.

Q. The what?

A. Vogelgram. That's -- published in 1990, a genetic sequence for colorectal cancer. So that's like a very important finding. Basically showed the sequence of molecular changes that take place in the progression of colon cancer from the normal cell to the cancer cell. So that is an extremely important discovery.

Kinzler I believe did the same thing in his lab as his postdoc for a different tumor. So I don't remember which tumor he did. He had several postdocs who basically did the Vogelgram for other tumors, like the pancreas cancer or for head and neck cancer or for other cancers. I don't remember which one Kinzler did. So he did the same thing.

I don't remember how Papadopoulos plays into that, but somewhere, but I've seen his name on some of the papers as well, and likewise Pardoll also did something similar, so they were all involved in this and they're all on multiple papers together, but mostly, again, in this molecular genetic series of studies on colon cancer or pancreas or other

cancers. Nothing to do with what we're talking about today.

THE WITNESS: Sorry.

Q. MSI is a molecular genetic marker; correct?

A. MSI is a? A molecular genetic marker? Yes.

Q. Are you aware of Dr. Luis Diaz's reputation at all?

A. Only insofar as he was involved with this 2015 paper, but beyond that, I don't really know.

Q. Is that the same for Dr. Le?

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

A. Dr. Le I don't know at all. Dr. Diaz I think I've heard a couple of times in terms of treatment of colorectal cancer, but Dr. Le I don't know at all.

Q. And do you know the reputation of Dr. Topalian at all?

A. No.

Q. I just want to look at paragraph 15 of your declaration. Let me know when you're there.

A. Okay.
Q. And in paragraph 15, you say that in forming your opinions expressed in your declaration, you reviewed the following documents and materials, and there is a list that goes onto the next page; is that right?
A. Yes, yes.
Q. And what do you mean by "reviewed"?
A. I read them. I'll say some of them I didn't read quite as thoroughly as some of the others, but I certainly looked at all of them.
Q. Are there any that you read more thoroughly than others?
A. I guess the ones that are listed were read more thoroughly than some of the ones that aren't listed.
Q. By "some of the ones that aren't listed," are you talking about the materials in appendix A that's at the end of the list here in paragraph 15?
A. Yes.
Q. And I think we can turn to the appendix A so we're all talking about the same thing, so on page 89 of your declaration or

page 90 of the exhibit.

A. Okay.

Q. So did you read all of the materials listed here in appendix A?

A. Well, again, I certainly looked at everything that was in Exhibit A, but some of these things I didn't read in depth or, you know, study closely.

Q. Did you review or rely on anything that isn't in paragraph 15 and appendix A in forming your opinions for this case?

A. I may or may not have. Occasionally I might have Googled something just to fill in a blank on something where I didn't remember a word or fill in some fact, just because my memory doesn't remember or just to make sure I knew what the word meant or needed to look up exactly what an acronym stood for or something like that, but beyond doing something like that, no.

(Clarification requested by the stenographer.)

A. Beyond that, the answer is no.

Q. Do you remember off the top of your head what you had to like Google?

A. Not off the top of my head, no. I do like to look things up to make sure I refresh myself on things that I don't know, and I don't remember everything of course. So I do -- I do that a fair amount, but will look in -- I don't know if you're familiar with UpToDate. So I look things up there occasionally.

(Clarification requested by the stenographer.)

THE WITNESS: I'm sorry.

A. I look in UpToDate occasionally to refresh myself on clinical things, but I don't think I had to do that very much here.

Q. What's UpToDate?

A. UpToDate is an online, I'll use the word, textbook of medicine. No one buys textbooks anymore. I don't think I've bought a textbook in 10 or 12 years, but everything is in -- UpToDate is everything in medicine that you want to know, and if you bring it up, you know, if you go to its site and put in the search term, whatever disease it is or something like that, it will bring up the item, and then if you read there, it has

almost everything in it up-to-date, more or less, plus any references that you may want to know. It's really remarkable how good it is, and all of my colleagues I think use it as their main source of information on clinical matters.

Q. Which of the documents here in paragraph 15 did you identify yourself?

A. In the paragraph we were just in?

Q. (Indicating.)

A. I don't believe any of them.

Q. Who provided you with the documents listed in paragraph 15 in appendix A?

A. The attorneys in the case.

ATTORNEY McCORMICK: I think it's a good time for another break, if that's all right with you?

Okay. We can go off the record.

CERTIFIED STENOGRAPHER: Off the stenographic record at 11:13 a.m.

(Whereupon, a recess is taken.)

CERTIFIED STENOGRAPHER: Back on the stenographic record at 11:33 a.m.

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, did you discuss the

substance of your testimony with counsel during the break?

A. No.

Q. And I have heard you coughing during this deposition. I want to make sure you're still okay to give truthful, complete, and accurate testimony today?

A. I'm fine. The coughing is I don't know what. It has nothing to do with anything.

Q. Okay. Good to hear.

I want to talk about clinical trials again, okay?

A. Okay.

Q. A skilled artisan would understand that just because a therapy resulted in a positive outcome in one clinical trial, does not mean it will result in a positive outcome in subsequent trials; right?

ATTORNEY RATLIFF: What time frame are we talking?

(No response.)

ATTORNEY RATLIFF: If you're not going to answer my question, I object to the form of your question.

A. That is true.
Q. Dr. Neugut, do you agree that prior to the clinical trial described in MSI high study record, only one patient had responded to a PD-1 blocker?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I don't know how many patients had responded previously to PD-1 blockers.
Q. Are you aware of any patients that had responded to PD-1 blockers before the MSI high study record?
A. Well, there is the one case that they reference in their paper and that's been sort of talked about all the time, the one guy who had a complete response and a prolonged complete response to the drug. I don't know if there were others and either they weren't written up or they were in other papers or whatnot. I don't even know.
Q. So you're aware of one patient that responded to a PD-1 blocker before the MSI high study record; correct?
A. Yes.

Q. And you are not aware of any other patients that responded to a PD-1 blocker before the MSI high study record?

A. You mean it was published, so correct.

Q. So I want to look at that publication regarding the one PD-1 -- the one patient that responded to the PD-1 inhibitor, okay?

A. Okay.

Q. So I'm going to hand you Exhibit 1057.

(Whereupon, document previously marked MERCK EX 1057, is received and marked as Exhibit 1057 for Identification.)

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, do you recognize Exhibit 1057?

A. Yes.

Q. Exhibit 1057 is an article titled: Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody; is that right?

A. Yes.

Q. And the first author of Exhibit

1057 is Evan Lipson.
Do you see that?
A. Yes.
Q. So if I refer to this as the Lipson article, will you understand I mean Exhibit 1057?
ATTORNEY RATLIFF: I object to the form of the question.
A. Yes.
Q. Do you see in the author's section of Exhibit 1057 Drew Pardoll and Suzanne Topalian?
A. Yes.
Q. And, Dr. Neugut, Pardoll and Topalian are inventors of the '393 patent claims; correct?
ATTORNEY RATLIFF: I object to the form of the question.
A. Yes.
Q. And is the Lipson article -- does it reflect the one cancer patient that you're aware of that responded to PD-1 inhibitors?
A. Yes.
Q. And if we could turn to page two of the Lipson article.

Down at the very bottom on the second column, under the heading: Durable complete response in colorectal cancer.

Do you see that?

A. Yes.

Q. And it does mention there in the very bottom of the second column of page two: Microsatellite instability, MSI, high genotype.

Do you see that?

A. Yes.

Q. Nowhere in this section or anywhere in this Lipson article does it say that the patient responded because of their MSI high status; does it?

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

A. I'm not understanding the question. It says he's MSI high, but it doesn't say he responded because he was MSI high. Is that the question?

Q. (Indicating.)

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

A. Well, you wouldn't write that here anyway. You would put that in the discussion I assume. So do you want to look at the discussion?

Q. Sure. We can look at the discussion.

ATTORNEY RATLIFF: For what purpose are we looking at the discussion?

(No response.)

ATTORNEY RATLIFF: If there is a question pending, I object to the form of the question.

Q. Dr. Neugut, I just want to clarify, the Lipson paper is talking about one MSI high CRC patient who was treated with a PD-1 blocker before the MSI high study record; is that your understanding?

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

A. I don't know when the patient was. I didn't see the date. Was it before the MSI high study record?

Q. So Exhibit 1057, the Lipson paper, was published January 15, 2013.

Do you see that? I'm sorry, it was

published online first, November 20, 2012.
A. Yeah.
Q. Do you see that?
A. Uh-huh, yes, uh-huh. Okay.
Q. And reported in the Lipson article is one CRC patient who was treated with a PD-1 inhibitor and had a durable complete response; correct?
A. Yes.
Q. And we were looking at the discussion section to see if anything in the discussion section mentions that that one CRC patient treated with a PD-1 inhibitor responded because they were MSI high?
A. Yes.
ATTORNEY RATLIFF: If -- okay.
Is there a question pending?
ATTORNEY McCORMICK: I'm giving Dr. Neugut a chance to read the discussion section so he can answer my question.
ATTORNEY RATLIFF: I don't know what the question is. So I object to the form of the question.
A. All right.

BY ATTORNEY McCORMICK:
Q. Did you finish reading the discussion section of the Lipson article?
A. Yes.
Q. And do you see anything in there about the one CRC patient who was treated with a PD-1 blocker responding because of their MSI high status?
A. No, it makes no reference to it.
Q. And is it true that in 2012, when this article published, testing for MSI high status was routine?
A. Was what?
Q. Routine?
A. I'm going to have to say I don't recall that far back if it was or wasn't. It might have been. I don't recall.
Q. This morning we were talking about testing for MSI high status in 2015.
Do you recall that?
A. Yes.
Q. And one of the reasons that you might have tested for MSI high status was to know if the patient had Lynch syndrome; is that right?

A. Yes.
Q. So is it possible that this CRC patient referred to in the Lipson article was tested for MSI status in order to understand their Lynch syndrome status?
ATTORNEY RATLIFF: I object to the form of the question.
A. It's possible.
Q. The Lipson article evaluates the PD-1 status of the tumor; correct?
A. Yes.
Q. And looking at page three of the exhibit, the second column at the very top.
A. Yes?
Q. The authors are -- the authors state: We have previously reported preliminary evidence for a correlation between tumor cell membranous PD-L1 expression and the likelihood of response to anti-PD-1 therapy; is that right?
A. Yes.
Q. And in that discussion that I just read, the authors aren't talking about MSI status; right?
ATTORNEY RATLIFF: I object to the form

of the question.
A. Correct.
Q. And in the Lipson article, that patient that was treated with an anti-PD-1 inhibitor, it's not pembrolizumab that they were given; right?
A. Correct.
Q. Do you know which drug they were given?
A. I believe it's nivolumab, but I'm not 100 percent sure.
Q. In 2012, at the time of the Lipson article, a POSA didn't know that pembrolizumab had treated MSI high cancers; correct?
ATTORNEY RATLIFF: I object to the form of the question.
A. In 2012? I don't know if he would have known about pembrolizumab. Might have had some inkling of -- he, I think, would have thought that immunotherapy might do it, but not necessarily pembrolizumab.
Q. And why would a POSA have some inkling that immunotherapy might treat MSI high cancers?
A. I think some of the articles that I

reference in my declaration alluded to that.

Q. Which articles?

A. Pernot and the MSI high study record itself would have implied it.

There was a press release from Galactica that I reference in 1084 that refers to several trials going on at the time that referred it, that's not in 2012, but it's still prior to the relevant time frame that we're talking about of the patent. So I think there you have a few examples of publications or documents that would have told the POSA and from which the POSA could have inferred or learned that the use of PD-1 inhibitors in immunotherapy would have been effective in MSI high patients.

Q. So those are a few examples, the Pernot article, MSI high study record, and the press release. Are there any others from which a POSA would have learned or expected that a PD-1 inhibitor would be effective in MSI high patients?

A. Tougeron.

Q. Is there an exhibit number for that one?

A. 1036.
Q. Thank you.
A. That's about it.
Q. Perfect. Thank you.
Dr. Neugut, I'd like to go back to the MSI high study record, Exhibit 1005.
ATTORNEY RATLIFF: I've got it.
Q. Do you have Exhibit 1005 in front of you?
A. Yep.
Q. The MSI high study record is a clinical study announcement. It's not a clinical study report; correct?
A. Yes.
Q. And the MSI high study record in Exhibit 1005 is a protocol posting; right?
A. Yes.
Q. The MSI high study record in Exhibit 1005 reflects a hypothesis to be tested?
ATTORNEY RATLIFF: I object to the form of the question.
A. Yes.
Q. And at the time the MSI high study record in Exhibit 1005 was posted, the

protocol had not been performed; correct?
A. Had not been performed, no.
Q. At the time the MSI high study record in Exhibit 1005 was posted, the protocol had not been performed; correct?
A. Correct.
ATTORNEY RATLIFF: I --
Q. At the time the MSI high study record was first posted, oncologists could not know the results; right?
A. Well, we've discussed this a little bit. They could not know the exact results, but as I said, they could anticipate that there would be -- that the drug would be efficacious.
Q. And that's the opinion that you're giving as part of this; right?
A. Yes.
Q. Is there anything in the MSI high study record in Exhibit 1005 that tells a POSA that the protocol will be successful or have a positive outcome?
A. No.
Q. If the clinical trial posted in the MSI high study record had been halted once it

started, oncologists would have no way of knowing whether the treatment would have a positive outcome; correct?

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

A. You mean if it had been halted before it was completed, then they would not have known the exact results of the outcome, right.

Well, I suppose if it had been halted before any data was collected, then yes. I suppose if they have partial data, they might have known something. So I don't know exactly what they would have known.

Q. Do you understand that FDA requires posting protocols on ClinicalTrials.gov before researchers can run a human clinical trial?

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

A. Yes.

Q. And this MSI high clinical study record in Exhibit 1005 was posted on ClinicalTrials.gov; correct?

A. Yes.

Q. And Hopkins was required by FDA to post the MSI high study record on ClinicalTrials.gov before conducting the protocol; right?

ATTORNEY RATLIFF: Wait. You're asking about Hopkins and Merck or Hopkins alone?

I object to the form of the question.

A. I'll agree to that point, that it was really Hopkins and Merck together who posted it.

Q. How do you know that?

A. They collaborated in the trial.

Q. So if you turn to page three of Exhibit 1005 under the section sponsor collaborators.

A. Yep.

Q. The sponsor is Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; correct?

A. Yes.

Q. And the responsible party here is the sponsor?

A. Yeah.

Q. Meaning Johns Hopkins; correct?

A. Correct, and the collaborator was

Merck Sharp & Dohme.

Q. And if you go to the last page of the MSI high study record, contacts and locations.

Do you see that?

A. Yes.

Q. And the principal investigator for the study protocol shown here in the MSI high clinical study record is Dr. Dung Le; right?

A. Yes.

Q. And Dr. Dung Le is at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; correct?

ATTORNEY RATLIFF: I object to the form of the question. You keep saying Young Le.

A. Yes. It's Dung Le, right.

Q. She says it Young.

A. Oh, she does?

Q. She does.

A. I guess there is good reason for that.

Q. What's your understanding of Merck's contribution to the study here in the MSI high clinical study record?

A. I don't have any knowledge of

exactly how the collaboration was conducted. As I said in an earlier answer to another question, most studies, most trials nowadays involve a number of collaborators.

Obviously, Dr. Le was the principal investigator and had overall responsibility for the conduct of the study, but then there are multiple people who are listed as collaborators or investigators on the study, and exactly what each one contributed or what each one did, I have no way of being able to describe or to be aware of.

Q. So FDA required Hopkins and Merck to post the clinical study protocols shown here in the MSI high clinical study record before they could run the study; correct?

A. To post it on ClinicalTrials.gov, yes.

Q. Is it your understanding that it's necessary to post the study announcement on ClinicalTrials.gov to get human clinical data?

A. To get human clinical data?

Q. (Indicating.)

A. To be honest, I don't know what you mean by that.

Q. To run a clinical trial in humans, is it your understanding that you have to post the protocol that you're going to run on ClinicalTrials.gov before you run the clinical trial?

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

A. Well, as you said, the FDA demands it. So it's required that you do it. That's, I don't want to say, the law, but that's required. I think they want the public to be aware of all the trials, and they also don't want -- they don't want -- they don't want redundancy in trials. So that's a reason why it's done as well. So this way everyone knows here is a trial of, in this case, for example, MSI high colon cancer, and so if someone else were planning such a study, they would or they should look at the website and see that such a study is planned, here is how it's going to be done, and they shouldn't exactly do the same thing or whatever or at least they should be aware of it so they don't recapitulate it exactly or trip over each other's feet and stuff like that.

I mean, also the other reason the FDA requires it is so that patients can be aware of it, so that if there is someone in Chicago who is looking for a trial because they had metastatic colon cancer and they're desperate, so they go to ClinicalTrials.gov and look around for trials on the website.

If they put in their characteristics, they'll find out in Baltimore there is a trial going on and they can travel to Baltimore and call Dr. Le or whatever and try to get into the trial, if they want to do that.

Q. Do you know if it's required to post a protocol on ClinicalTrials.gov before running a clinical trial?

A. I'm sorry, have you not asked me that now three times?

ATTORNEY RATLIFF: I'll just note for the record that counsel is shaking her head that to your question about if she's asked you the question three times.

A. I mean, wasn't this the same question you asked me a minute or two ago?

Q. Yes. Dr. Neugut, I'm trying to

make sure that I understand your testimony clearly and also that the judges in this case understand your testimony clearly.

A. So the answer is, yes, it is required by the FDA that all clinical protocols for trials be posted on ClinicalTrials.gov, and the patent board should be aware of that. It wasn't posted frivolously, and I don't know if they were planning not to post it and to keep it secret otherwise, but yes, it is required that it be posted.

Q. And if Hopkins or Merck wanted to keep a clinical study secret, they could do that; right?

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

A. If that's your point, yes, you're correct. They could not -- they could not keep a trial secret. I mean, if putting it on ClinicalTrials.gov means not keeping it secret, you're right, they could not keep it secret. They would have to post it on ClinicalTrials.gov, so anyone who wanted to, could look it up or find out about it and know

about it.

Q. Thank you.

Now, clinical study protocols outline an experiment; right?

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

A. I'm sorry, I didn't hear the question clearly.

Q. Clinical study protocols outline an experiment; correct?

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

A. Yes, they do.

Q. The MSI high study record in Exhibit 1005 does not disclose how the MSI high status will be tested; is that right?

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

A. It doesn't state exactly what methodology should be utilized as I've said now once or twice. It does imply that it has to be tested, otherwise you wouldn't know who was MSI high and who was MSI negative, but it does not explicitly state what was required to be done in order to make that determination.

Q. So the MSI high study record does not disclose having carried out an immunohistochemistry test on the patient sample?

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

A. No, it does not explicitly say that they have to have immunohistochemistry. They could have PTR. They could have next generation sequencing. They could have another method done.

Q. Those other methods that you mentioned, that PCR or next gen sequencing, those are not disclosed in the MSI high clinical study record; right?

A. None of them are disclosed, but any of them would fulfill the requirement of determining the MSI status of the patient before they undergo pembrolizumab therapy.

Q. And the MSI high study record does not disclose that the biological sample being tested for MSI high status is a body fluid from the patient; right?

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

A. It does not disclose that, but also it could just as well be a body fluid and the POSA would have totally appreciated that, that would be just as well as having a tumor specimen or not. Either one would be suitable or adequate for doing whatever test was necessary in order to determine MSI status.

Q. The MSI high study record does not disclose that the protocol results in being effective in promoting progression-free survival in multiple human subjects whose colorectal cancer is MSI high or mismatch repair deficient; right?

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

A. I'm sorry, you lost me on that question.

Q. The MSI high study record does not disclose any results from carrying out the protocol; correct?

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

A. No, it does not.

Q. And the MSI high study record does not disclose any preclinical results, like

animal testing or in vitro testing; right?
A. No, it does not.
Q. Are you aware of any animal methods that could be used to test PD-1 inhibitors for MSI high tumors?
A. No, I'm not familiar with them.
Q. You said that you reviewed the prosecution history for the '393 patent; right?
A. Yes.
Q. Are you aware that the Patent Office considered the clinical study record as part of the -- part of evaluating the patentability of the '393 patent?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. Could you repeat the question?
Q. Are you aware that the Patent Office considered the MSI high clinical study record as part of evaluating the patentability of the '393 patent claims?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.

A. Yes.
Q. And you think the Patent Office got it wrong?
A. Yes.
(Whereupon, document previously marked MERCK EX1006, is received and marked as Exhibit 1006 for Identification.)
BY ATTORNEY McCORMICK:
Q. Do you have Pernot Exhibit 1006 in front of you?
A. (No response.)
Q. Do you have Pernot Exhibit 1006 in front of you, Dr. Neugut?
A. Yes.
Q. Let's look at that.
Do you know what a claim limitation is, Dr. Neugut?
A. Could you repeat the question?
Q. Do you know what a claim limitation is?
A. It's -- yes, I do know, but I have to recollect. It's a part -- it's like you have separate paragraphs.
Q. Perfect. I will use that same understanding of what a claim limitation is

when we talk, okay?

You're not relying on Pernot, Exhibit 1006, for disclosing the "in response to" claim limitation; correct?

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

A. I don't believe so.

Q. And just so we're all on the same page somewhat literally, you could have the '393 patent in front of you on the very last page looking at the claims.

A. On the very last page?

Q. That's right. Second-to-last page, sorry.

A. Second-to-last page. Yeah.

Q. And when I'm referring to the "in response to" limitation, I'm talking about the very last phrase of claim one and claim 14 where it says: In response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, comma, treating the patient with a therapeutically effective amount of pembrolizumab.

Do you see that?

A. Yes.
Q. So if I refer to that as the "in response to" limitation, will you understand what I just read is what I'm referring to?
A. Yes.
Q. And you are not relying on Pernot for disclosing the "in response to" claim limitation; right?
A. Correct.
Q. You are only relying on Pernot for the testing limitation; correct?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I'm sorry, could you repeat your question?
Q. You are only relying on Pernot for the testing claim limitation; correct?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
And, Dr. Neugut, I know that you're coughing, so you could take your time.
THE WITNESS: No, no, I'm fine.
A. I would say that I'm relying on

Pernot for the conduct of the clinical trial, which would involve both testing and then following up the testing with giving pembrolizumab in response to the results of the testing. I don't think it's limited to the testing.

Q. Is there anything else from Pernot that you're relying on --

A. No.

Q. -- for your opinions in this case?

A. No.

Q. Pernot does not disclose anti-PD-1 therapies; right?

A. No, correct.

Q. Pernot does not disclose that MSI high CRC patients would be promising candidates for PD-1 checkpoint blockade therapy; correct?

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

A. No, he does not.

Q. And Pernot does not disclose any relationship between MSI high CRC patients and their likelihood of responding to PD-1

checkpoint blockade therapy; right?

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

A. No, he doesn't make reference to it.

Q. And if I could direct your attention to page four of Pernot, the second column under the heading: Microsatellite Instability CRC is Associated with Immunogenic TAAs.

Do you see that?

A. Yes.

Q. And the Pernot article states that: Microsatellite instability MSI is associated with CRC in patients with Lynch syndrome, but also with sporadic cancer, in particular in elderly patients, and is observed in 5 percent of 25 percent of CRC patients depending on tumor stage.

Did I read that right?

A. Yes.

Q. And do you agree with that?

A. Yes.

Q. You can set that one aside.

ATTORNEY RATLIFF: Counsel, since you're switching gears and we're close to an hour, let's take our lunch break now.

ATTORNEY McCORMICK: That sounds good. We can go off the record.

CERTIFIED STENOGRAPHER: Off the stenographic record at 12:26 p.m.

(Whereupon, a luncheon recess is taken at 12:26 p.m.)

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A F T E R N O O N S E S S I O N
(1:06 p.m.)
CERTIFIED STENOGRAPHER: Back on the stenographic record at 1:06 p.m.
BY ATTORNEY McCORMICK:
Q. Dr. Neugut, did you talk about the substance of your testimony during the lunch break?
A. No.
Q. Do you have Exhibit 1007, Chapelle, in front of you?
A. I'm sorry, which? Oh, 1007?
Q. Yes.
A. Yes.
Q. As part of your opinions for this case, you're only relying on Chapelle, Exhibit 1007, for disclosing testing of a biological sample; is that right?
ATTORNEY RATLIFF: I object to the form of the question.
A. I don't recall what exactly I said about it, but I don't know if there was anything else in the article that was important.
Q. You are relying on Chapelle for

disclosing testing a biological sample; right?
A. Yes.
Q. And you're not relying on Chapelle for disclosing the "in response to" claim limitation; right?
A. That's correct. I am not.
Q. And Chapelle did not suggest giving a patient pembrolizumab in response to determining a patient's tumor as MSI high; correct?
ATTORNEY RATLIFF: I object to the form of the question.
A. The truth is that he does not discuss the use of immunotherapy in the context of MSI colorectal cancer.
Q. And if I could point your attention to kind of the middle of the abstract, seven lines down the sentence: Of all colorectal cancers, CRCs, 15 percent to 20 percent display MSI or abnormal IHC, often referred to as a -- as microsatellite instability MIN pathway.
Do you see that?
A. Yes.
Q. And do you agree with that?

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

A. Yes. As I said, since we're talking primarily about metastatic colorectal cancer, that percentage actually does not apply to metastatic colon cancer. That percentage is for all colorectal cancer, and that number has been repeated several times now, and it's really not accurate. Well, it's accurate for what it is accurate for, but it's not accurate for metastatic colorectal cancer. The number is significantly smaller.

If this is relevant or important to us, the number is significantly smaller for metastatic colorectal cancer for various reasons.

Q. And you said that MSI high for metastatic colorectal cancers is 4 percent; right?

A. 4 percent, 4 to 6 percent. I -- I -- I guess it depends on the study you read, but the number in my head is 4 to 6 percent.

Q. And if I can direct your attention to page three of Exhibit 1007, under the subheading: Clinical significance of MSI L --

A. I'm sorry, what page are you on?
Q. Page three.
A. Three?
Q. Correct.
A. Uh-huh.
Q. The very first sentence under the subheading: Clinical significance of MSI L --
A. Uh-huh.
Q. -- says: Around 15 percent of unselected CRC tumors are MSI high, MSI-H.
Did I read that correctly?
A. Yes.
Q. What does unselected CRC tumors mean?
A. I think that's what I was alluding to before. Unselected meaning all-comers, if you take all colorectal cancer then 15 percent are MSI high, but that would be like all stages, all colorectal cancers, everybody, but then subgroups you'll get different percentages depending on the subgroup you look at.
Q. If I could turn your attention to page five of Exhibit 1007, under the subheading: MSI M CRC prognosis.

Are you there?
A. Okay.
Q. And that second paragraph right at the very bottom of the second column on page five of Exhibit 1007, the first sentence says: Some recent studies have not found a better prognosis for patients with MSI CRCs.
Do you see that?
A. Yes.
Q. Okay. And this Chapelle article was published in 2010; right?
A. Yes.
Q. And do you agree with that statement, that some recent studies in 2010 have not found a better prognosis for patients with MSI CRCs?
A. I wouldn't be able to address that. I mean, he makes a reference to publications which I guess I would have to -- yeah, I guess I would have to read the two papers he references, and I don't know in general what he's talking about or what he's referring to. Even if two papers didn't find a similar prognosis for MSI high patients, that would go against I would say the bulk of studies.

Q. On the next page, page six of Exhibit 1007, under the subtitle: MSI and CRC Treatment, Chapelle discusses in the second paragraph: The first major study indicating that patients with stage two or stage three MSI CRCs did not benefit from FU-based adjuvant therapy, while patients with stage two or stage three MSS or MSIL CRC did was Redick, et al., in 2003.

Did I read that right?

A. Yes.

Q. And he goes on to report that: This study indicated that the overall survival for patients with MSI tumors who received FU was worse than for those who did not; correct?

A. Yes.

Q. Is Chapelle reporting that the MSI high patients had a worst outcome on the FU treatment?

A. I don't know. I would have to read the paper. As I said, patients who are MSI high don't benefit from 5FU. The truth is the tumor is biologically as if it already got 5FU, so that's why it has a better prognosis. It's as if it already got 5FU, so overall it's

better off. The prognosis is superior for MSI high patients, but it does not -- so getting 5FU is a negative. You're being treated for no purpose and you're getting the side effects of 5FU. So I suspect that's what really goes on in this context.

Q. And if the stage two or stage three MSI patients don't benefit from getting FU, what other treatment option did they have before 2015?

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

A. We discussed this in the morning. They could get a full FOLFOX. So the common regime, the standard regime for colon cancer is a regimen called FOLFOX, which is a combination of two drugs, 5FU and oxalitlatin. So 5FU is the main drug in that combination.

Theoretically under some circumstances, you might get 5FU alone without the oxalitlatin, and the oxalitlatin, 75 percent of the benefit of FOLFOX comes from the 5FU, so under some circumstances you could get the 5FU without the oxalitlatin, if you had reason to, but in the context of -- we've

1 been saying of MSI positive colon cancer, you
2 wouldn't get any benefit from 5FU alone, but
3 if you give the 5FU with oxalitlatin, then
4 you've got a good regime.
5 Again, you sort of restored --
6 you've got a good regime again so you can give
7 the full regime, but you can't give 5FU alone.
8 So if there were a reason why you didn't want
9 to give oxalitlatin in the context of a
10 patient who is MSI high, it forces your hand
11 to give the full regime even if you didn't
12 want to.
13 So, for example, sometimes in an
14 elderly patient, oxalitlatin has a lot of side
15 effects, so I might not want to give
16 oxalitlatin to an 80-year old lady. So I
17 might want to give just 5FU alone and let her
18 have 75 percent benefit without getting the
19 side effect of oxalitlatin, but if you were
20 MSI high, I would feel compelled to give her
21 full the FOLFOX regime and let -- let her
22 hazard the side effects of the oxalitlatin and
23 have to, you know, take her chances with the
24 full regime.
25 Q. Was there any other treatment

1 option for metastatic MSI CRC patients besides
2 the FOLFOX?
3 A. Oh. Well, nowadays, again,
4 depending on other tumor markers, there are
5 other treatments that you might be sensitive
6 to if you have other markers. So that's a
7 possibility, and there are two or three new
8 oral -- and again, now we're talking about in
9 2024 --
10 Q. And I -- and if I may --
11 ATTORNEY RATLIFF: Wait. Wait. Wait.
12 Don't cut him off.
13 A. So in 2024, there are new oral
14 agencies, wouldn't have been around, you know,
15 Chapelle's time or -- you know, but so, yeah,
16 now there are new oral drugs you could give
17 patients, but again, back to classical, you
18 know, real chemotherapy, most chemotherapy
19 depends on 5FU so --
20 Q. So in 2015, were there any other
21 treatment options for metastatic MSI CRC
22 patients besides FOLFOX?
23 ATTORNEY RATLIFF: I object to the form
24 of the question.
25 A. There were others, but they were

all 5FU dependent. So, in other words, 5FU was always the core. So there are other regimes, because you could add other drugs besides oxalitlatin to them, but always it would be with 5FU, plus something else.

Q. Okay. You can set Chapelle aside.

(Whereupon, document previously marked MERCK EX1008, is received and marked as Exhibit 1008 for Identification.)

BY ATTORNEY McCORMICK:

Q. And do you have Exhibit 1008, Steinert, in front of you?

A. If you'd give me a moment.

Q. Of course.

A. Okay.

Q. You have Steinert in front of you?

A. Yes.

Q. As part of your opinions for this case, you rely on Steinert for disclosing testing body fluid; correct?

A. Yes.

ATTORNEY RATLIFF: And, Counsel, do you have a copy of Steinert for us?

ATTORNEY McCORMICK: Apologies.

ATTORNEY RATLIFF: No worries.

ATTORNEY McCORMICK: For you, Mr. Court Reporter.

BY ATTORNEY McCORMICK:

Q. As part of your opinions for this case, you do not rely on Steinert for the "in response to" claim limitation; correct?

A. No.

Q. And Steinert does not suggest giving a patient pembrolizumab in response to determining the patient's tumor is MSI high; correct?

A. Doesn't refer to that, no.

Q. Steinert is about characterizing circulating tumor cells in colorectal cancer patients; right?

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

A. That's correct.

Q. All right. We can set Exhibit 1008 to the side.

(Whereupon, document previously marked MERCK EX1009, is received and marked as Exhibit 1009 for Identification.)

BY ATTORNEY McCORMICK:

Q. And as you might have guessed,

let's look at Exhibit 1009, Benson.
Do you have that in front of you?
A. Yes.
ATTORNEY McCORMICK: Sorry, counsel. I'm looking for a copy. Oh, hiding.
Q. Dr. Neugut, you have Exhibit 1009, the article by Benson in front of you?
A. Yes.
Q. What is this Benson publication?
A. These are what are called the NCCN guidelines from 2014.
Q. And are these guidelines you would review in the normal course of your practice?
A. Yes. They're guidelines that are widely utilized within oncology for clinical decision-making.
Q. And as part of your opinions for this case, you rely on the Benson publication for two points; correct?
A. For what?
Q. Two points?
A. I don't recall where I referred to it. I don't recall where I referred to it. I would have to look it up.
Q. And you're looking in your

declaration?
A. Yes.
Q. Okay. Let me know when you're ready.
A. Thank you. Okay.
Q. As part of your opinions for this case, you relied on Benson for disclosing the patient's cancer having progressed following different cancer therapy; correct?
A. Yes.
Q. And you also relied on Benson for disclosing the patient's cancer being metastatic or metastatic colorectal cancer; correct?
A. Yes, we sort of reviewed this briefly this morning, that the POSA would have understood and no one would have thought otherwise that in order to be in a clinical trial, a patient with advanced colon cancer would have been both metastatic and would have had to have progressed on two prior treatments, one of which would have been FOLFOX and another one is known as FOLFIRI.
Q. Pembrolizumab is not recommended as a treatment for colon cancer anywhere in

Benson; right?
A. That's correct.
Q. As a part of your opinions for this case, you do not rely on Benson for your opinions regarding claim -- patent claims 37, 39, and 41; correct?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. Could you repeat the question?
Q. As part of your opinions for this case, you do not rely on Benson for your opinions regarding claims 37, 39, and 41; correct?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I believe it also refers to those claims.
Q. And can you point me where in your declaration you see that?
A. On page 70 under .5, each and every limitation of claim seven, 20, 29, 30, 32, 34, and 36 to 42 found in the MSI high study record or the MSI high study record in view of

Pernot in combination with Benson.

Q. Benson does not disclose any results from giving pembrolizumab to the metastatic CRC patients; correct?

A. No, it does not. You know, the NCCN guidelines are like -- they're vanilla. You know, they are exactly what the straightforward practice is at the time that they're being written. So they would not deviate from the straight and narrow, and at that time giving pembrolizumab would have been -- it wasn't FDA approved. It wasn't tested. It wasn't anything.

Q. That context is helpful. Thank you.

(Whereupon, document previously marked MERCK EX1010, is received and marked as Exhibit 1010 for Identification.)

BY ATTORNEY McCORMICK:

Q. Do you have Salipante, Exhibit 1010, in front of you?

A. I will get it.

Q. Okay. Great. Let me know when you've got it.

A. Okay. I have it.

Q. And as part of your opinions for this case, you're relying on Exhibit 1010 for disclosing methods of testing for MSI status; right?

A. Yes.

ATTORNEY RATLIFF: And, counsel, do you have a copy of Salipante for us?

ATTORNEY McCORMICK: I do.

Q. And you rely on Salipante for your opinions in this case for disclosing methods of testing MSI status because those methods aren't disclosed in the MSI study record; right?

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

A. Well, again, the MSI study record does not disclose explicitly the methods by which one could test or for the -- for MSI, but again, the POSA would have understood that one had to test, and the exact method or which precise method one used really doesn't matter. One could have used the immunohistochemistry on tumor specimen or one could have done PCR or one could have used body fluid for the

POSA, and for clinical practice it really makes no difference which one of those you use, and Salipante at least describes the method -- two of the methods that could be used as alternatives to tumor specimen analysis and the POSA would have been aware of it.

Q. And you're not relying on Salipante for disclosing the "in response to" claim limitation; correct?

A. No.

Q. "No" meaning correct?

A. Meaning correct. While it is true that the therapeutic use of or the use of pembrolizumab would have been in response to the testing that Salipante describes according to the MSI study record, Salipante himself does not make any illusions to the use of immunochemistry -- immunotherapy or to pembrolizumab specifically.

(Whereupon, document previously marked MERCK EX1011, is received and marked as Exhibit 1011 for Identification.)

BY ATTORNEY McCORMICK:

Q. Do you have Hamid, Exhibit 1011, in

front of you?
A. I'm sorry, which paper is that?
Q. Hamid.
A. Oh, Hamid.
Q. The Exhibit 1011.
A. I have it.
Q. And as part of your opinions in this case, you rely on Hamid only for the claim limitation of administering pembrolizumab intravenously; correct?
ATTORNEY RATLIFF: I object. Sorry, you were coughing, Doctor. I object to the form of the question, as well as to the premise of the question.
A. Well, in this case, I think -- I'm sorry, can you repeat the question?
Q. As part of your opinions for this case, you rely on Hamid only for the claim limitation of administering pembrolizumab intravenously; right?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. I think there are two aspects to Hamid. One is what you said, which is that it

1 indicates that pembrolizumab is given
2 intravenously or would be given intravenously,
3 which, again, everyone already knew that at
4 the time. The POSA would know that as well,
5 but in addition, it talks about the use of
6 pembrolizumab for melanoma and it's
7 successfully used for melanoma, and I think
8 that would have been an encouragement to the
9 POSA, to the conduct of the trial, in the
10 context of MSI high colorectal cancer, because
11 there is transitions or there is transference
12 of drug from one tumor to another. So the
13 fact that immunotherapy was positive or useful
14 in one context, would have been certainly
15 encouraging for its use in different context.
16 Q. And when you say it would have been
17 encouraging for use in a different context, do
18 you mean any different tumor type or
19 colorectal cancer specifically?
20 A. Well, certainly if one were
21 entertaining the use -- if one were setting up
22 a trial to utilize it in MSI colorectal
23 cancer, then I think any investigator or
24 anyone looking at that would have felt, Oh,
25 look, it was used in melanoma successfully.

The odds or the probability that it would be successful or efficacious in our context as well is more likely because of that. If the drug had never been useful in any cancer, the odds out of the blue that it's going to be successful in MSI colorectal cancer would certainly be much lower. So the fact that it had been used in melanoma with great success was certainly a very positive sign or a very positive signal to the investigators I think for the MSI colon cancer and it would have been to a POSA as well.

Q. Hamid doesn't talk about MSI high status; right?

A. I don't believe that it does, no.

Q. And Hamid doesn't talk about colorectal cancer; correct?

A. No, it does not.

Q. The only dependent claims, patent claims that you rely on for Hamid are the ones that have the IV administration limitation; correct?

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

A. To be honest, I don't really

understand that, because -- why it is that way, because isn't it given intravenously in all the claims? So why it's limited to those in particular I don't know, but that's true, the way I have it written here, but it's always given intravenously, so -- but yes, according to the way that my declaration is written.

Q. Okay. Thank you.

Dr. Neugut, do you agree that Merck did not invent pembrolizumab?

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

A. I have no idea who invented pembrolizumab.

Q. The FDA approval for Keytruda for MSI high cancers was the first approval based on a biomarker; right?

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

A. The first approval of what for a biomarker?

Q. FDA approval for Keytruda, for MSI high cancers was the first approval of a

cancer drug that was based on a biomarker instead of the site of the cancer; is that right?

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

A. No.

Q. Why do you say that?

A. Because it's not true.

Q. Please tell me more about why that's not true.

A. Or at least not how I would understand this, but maybe I'm -- give tamoxifen for estrogen receptor positive breast cancer, to me that's a biomarker being given for -- a drug being given for a biomarker.

Q. Okay. Are you familiar with the term "tumor agnostic"?

A. Yes.

Q. What does that mean to you?

A. Oh, okay. If you're going to use the term that way, tumor agnostic means that we're giving a drug purely on the basis of a marker and not on the basis of the site of the disease.

There are other drugs that are tumor agnostic, but I don't know which is the first. If MSI is the first, then okay. I don't know that -- I don't know if that's the first one, but yes, it is, or it's become tumor agnostic.

There are others that are also tumor agnostic, but so I don't know which is the first, but I don't know the answer to your question.

(Clarification requested by the stenographer.)

ATTORNEY RATLIFF: But I don't know the answer to --

A. I don't know -- that's the first one. So I didn't know exactly that's the first, but it is tumor agnostic.

Q. So Keytruda has a tumor agnostic indication for MSI cancer, MSI high cancers; correct?

A. Yes. I don't know if that was the way the original approval was given, but at this point it is.

Q. When the MSI high clinical study record was published, which was 2013, were you

aware that pembrolizumab had not been approved by FDA for any indication?

A. Yes.

Q. Are you aware that Keytruda has cured patients with advanced stage MSI high CRC?

A. I cure them all the time.

Q. You have seen advanced stage MSI high CRC patients cured with Keytruda?

A. Uh-huh. I'm sorry?

Q. Are you asking me to repeat the question?

A. Did you ask me a question?

Q. You have seen advanced stage MSI high CRC patients cured with Keytruda; right?

A. Yes.

Q. And those patients you've seen who have been cured with Keytruda, what do they think about Keytruda?

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

A. I don't know. I don't do -- we don't fill out surveys like that. I don't ask them questions like that. I -- I know that they like me, so I have no idea what they say

about the drug, but I assume they like it.

Q. Fair enough. Thank you.

Have you seen the Keytruda prescribing information?

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

A. I've never read the package insert, if that's what you're asking me.

Q. That is what I'm asking you.

How do you know how you can prescribe Keytruda if you haven't read the package insert?

A. So as to many cancer centers, we use computerized prescribing or chemotherapy order, order programs, software programs so that we don't screw up and kill someone. To be honest, you know, you don't want to screw up ordering chemotherapy. So everything we do is carefully preprogrammed.

So we -- to minimize the risk of misordering the wrong dose or never so -- so I just go to the correct website and put in the patient's -- you know, put the patient in and put it in for the right day and whatever and

then pull up -- and then when I tell the computer that I'm giving the patient chemo starting on a certain day, it asks which chemotherapy regime do you want to do, and then I go down to P and pull up pembrolizumab, and then it offers me a menu of exactly when I want it, and it has the dose and administration information already preprogrammed based on the patient's weight and height, and I can alter it, but the default is already in, and then I can review it, which I do carefully, of course, and then I sign off on it.

That may sound simplistic, but believe me, it's -- you can save a lot of lives.

Q. So in the system that you use, when you're prescribing Keytruda for patients, do you indicate that the patient is getting Keytruda because of their MSI high status?

A. It does ask the patient's diagnosis. So I don't know if it asks -- I do put in colon cancer. I don't know if I put in MSI high colon cancer.

The insurance company will ask, you

1 know, they have to get preauthorization for
2 chemotherapy because otherwise they don't get
3 paid and nothing happens without the
4 insurance. So I am certain that that gets
5 indicated and then forwarded to the patient's
6 insurance company and authorized, and it would
7 not get authorized if it wasn't -- and they
8 check if it's MSI high as opposed to MSI
9 negative. It would never be paid if it were
10 not MSI high.
11 Q. You said that you cure people all
12 the time with MSI high --
13 A. All right. Maybe that was an
14 exaggeration.
15 Q. I appreciate that. You cure people
16 using Keytruda, the MSI high CRC patients.
17 Before you had Keytruda, were you
18 curing MSI high CRC patients?
19 A. Curing a patient with a metastatic
20 solid tumor, it's a very rare phenomenon. I
21 would say in my career, which stretches back
22 40 years and encompasses thousands of
23 patients, I've cured seven. And with Keytruda
24 and MSI high colon cancer, I've probably cured
25 another seven in the last five years.

Q. That's great.
Is that computer system that you use for prescribing drugs set up to prescribe according to the prescribing information for the drug?
ATTORNEY RATLIFF: I object to the form of the question.
A. I assume they used the recommended dosing. Again, I -- I don't know if they're copying it off the label or where they're getting it from, but I know dosing -- sometimes I will use Google to check the dosing myself because I want to be sure also that it's right. I'm responsible, you know, and I do modify the doses on occasion, but I couldn't tell you -- I mean, a chief of pharmacy who puts the dosing in and it's all checked when we put it in the drug, you know, when we -- when a drug is entered into the system, it's very carefully done and everyone signs off on it, etc. So I couldn't tell you where the initial doses come from, but I assume they come off the prescribing information provided by the company.
Q. Were you aware that the FDA awarded

Keytruda a breakthrough therapy designation for using Keytruda to treat MSI high CRC patients?

A. No. I'm not surprised.

Q. Why do you say that?

A. Well, the survival benefit is impressive, I'm sure there was pressure on the FDA to give it what they call a fast track designation.

Q. Are you familiar with the breakthrough therapy designation the FDA gives drugs?

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

A. I didn't know there were breakthrough. I've always heard it called the fast track designation, but I assume it's the same thing, yes.

Q. Why would FDA feel pressure to give Keytruda the fast track designation for MSI high colorectal patients?

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

A. Normal time frame for getting the drug approved by the FDA is on the order of

years. So let us say you wait two years to get a drug approved, the number of patients who are not going to be treated and suffer during that time is certainly in the hundreds, and the drug, which has such a dramatic benefit, would really be unethical to -- or it would be detrimental to not fast track it and do something more rapidly. It's not done except in such dramatic circumstances.

Q. Dr. Neugut, are you aware that Keytruda has made Merck a lot of money?

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

A. Yes.

Q. Are you aware that Keytruda is the world's best selling drug?

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

A. I'm aware that it was at one time. I don't know if it still is, but I know that there was a time when it was the number one selling drug.

Number one in revenue. I don't

know if it's number one in the number of patients who are receiving it, but there are different ways to measure number one.

Q. I hear you.

Would you agree that some percentage of the Keytruda sales are going to patients with MSI high tumors?

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

A. I would not know how to break down Merck's revenues.

Q. Are you aware that Hopkins receives no money from Merck for Keytruda sales?

ATTORNEY RATLIFF: Are you representing that?

(No response.)

ATTORNEY RATLIFF: If you won't answer my question, I object to the form of your question.

A. I have no idea how much Merck -- how much Hopkins made or did not make on this.

Q. Part of your opinions for this case are that the posting of the MSI high study record invalidates these patent claims; is that right?

A. Yes.
Q. So is it your opinion that if you post a clinical study protocol, you can't get patent claims for that method of treatment?
A. I don't know. That's a legal question and I'm not a lawyer. So that's something you would have to ask the Paul Hastings' attorneys. I don't have a legal opinion in this case.
ATTORNEY RATLIFF: And, counsel, I would think whenever you're at a question, we've been going about an hour, so let's take a break.
ATTORNEY McCORMICK: I'm happy for a break.
We can go off the record.
CERTIFIED STENOGRAPHER: Off the stenographic record at 2:08 p.m.
(Whereupon, a recess is taken.)
CERTIFIED STENOGRAPHER: Back on the stenographic record at 2:28 p.m.
BY ATTORNEY McCORMICK:
Q. Dr. Neugut, did you discuss the substance of your testimony during the break with counsel?

A. No.
Q. I want to talk about clinical trials again with you, okay?
A. Whatever you'd like.
Q. Oncology clinical trials, they can take a long time to complete; correct?
A. Yes.
Q. Why is that?
A. Usually it's because the endpoint is -- the usual endpoint is survival and it takes a long time for people to die.
Q. And patients enrolled in oncology clinical trials, they don't pay to be enrolled in those clinical trials; right?
ATTORNEY RATLIFF: Wait. Every single clinical trial that ever existed, is that what your question is about?
(No response.)
ATTORNEY RATLIFF: If you're not going to answer my question, I object to the form of the question.
A. The point is accurate. There may be some trials where people actually pay, but generally speaking, trials are funded by someone or other, like a drug company or

government, and so they're usually done gratis to the patients. Very occasionally an insurance company will pay, but that's -- no, actually not infrequently, an insurance company will pay too.

Q. So generally speaking for oncology clinical trials, patients aren't paying to participate in the clinical trial?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. I'm sorry, I didn't hear the question.

Q. Generally speaking for oncology clinical trials, patients are not paying to participate in the clinical trial?

ATTORNEY RATLIFF: Objection. Asked and answered.

A. That is correct. Patients do not usually pay to be in a trial, although, again, that is not -- it really depends on the circumstances. There may be clinical trials where patients are paying -- where the clinical trial is sort of in the normal course of clinical events, and under those circumstances, they may pay in the same way

that they would pay for any other clinical therapy. That occurs.

Q. As far as you're aware, FDA does not pay companies to publish results from oncology clinical studies?

A. The FDA?

Q. (Indicating.)

A. I think the FDA expects investigators to publish their studies or the results of their studies, but it doesn't pay them to do it.

Whatever funding paid for the trial will usually have funding in it to pay for the publication and will expect the publication to emanate as an end product of the conduct of the trial.

Q. Is it your understanding that clinical trial data is kept confidential until publication?

ATTORNEY RATLIFF: Is your question as to every possible clinical trial that's ever been done?

(No response.)

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

A. It really depends on what data you're talking about. I mean, patient data is -- first of all, it's always confidential in the sense of being anonymized. So to that degree, it's, I don't know, confidential, but no, nowadays actually data is public and expected to be made available to other investigators to be able to utilize it for study.

There may be a delay time which gives the initial investigators a chance to get their data out and publish it first, but ultimately, I think they expect that data will be made available to other investigators so they can analyze it also.

Q. While -- generally speaking, while a clinical trial is ongoing, is it fair to say that only a limited number of people would have access to the data generated from that clinical trial?

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

A. Yes.

Q. Generally speaking, the sponsor of an oncology clinical trial keeps the records

resulting from that clinical trial; right?
ATTORNEY RATLIFF: I object to the form of the question.
A. I'm sorry, who did you say keeps the data?
Q. The sponsor of the clinical trial?
ATTORNEY RATLIFF: The same objection.
A. No.
Q. Why do you say that?
A. Because it's not true.
Q. Who keeps the study records then?
ATTORNEY RATLIFF: I object to the form of the question, as well as to the premise of the question.
A. Those who are conducting the trial keep the data.
Q. So those who are conducting a clinical trial keep the records from that clinical trial?
A. Yes. I mean, I should say that it really depends on the circumstances. Also, if it's under, for example, the NIH or something like that, then they may -- they have the right to monitor that and to come in and do audits and to do -- make sure that the data is

being kept correctly and ethically and there aren't any oversights, errors, etc.

Likewise, I mentioned earlier cooperative groups do many, many of the trials in the United States, and so cooperative groups have oversight over trials oftentimes and the drug companies have oversight over their own trials. If an institution, like a university, is conducting a trial under the -- in collaboration with a drug company, then the drug company certainly would have oversight or access to the data or to be able to audit the data as well.

Q. So clinical -- oncology clinical trial can take time to get enough eligible patients enrolled to power the study sufficiently; is that right?

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

A. Depends on the nature of the study. Sometimes as you say recruitment can be what delays or what takes time. Sometimes, as I said, it's waiting for the endpoint to occur, like waiting for people to die.

Q. And because it can take time to

recruit enough patients to carry out the clinical study, that can lead to additional time before results are reported; right?

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

A. Again, all these things take time. Everything -- all of these things can get -- getting an IRB approval can take time. You know, each thing adds its own layer of delay into the conduct and completion of the trial.

Q. And even after, generally speaking, a clinical trial is completed, researchers will continue to monitor clinical trial patients; right?

A. That will vary from trial to trial, but oftentimes, yes, and occasionally, no. It really depends on the nature of the trial. That question is not answerable as a general -- there is no hard and fast rule.

Q. You had mentioned that one of the endpoints you might be monitoring for an oncology clinical trial is how long it takes the person to die; right?

A. Yes.

Q. And that's a measure that endpoint, it can take some time; correct?
A. Yeah. Well, nowadays that's often not used anymore as a -- as an endpoint because it takes so long. So most studies now use an endpoint called progression free survival as the main endpoint and, in fact, I think this trial did as well.
Q. All right.
Dr. Neugut, I want to talk to you about your role in this case and preparing your declaration, okay?
A. Whatever you'd like.
Q. When were you first contacted about this case?
A. I don't recall.
Q. Was it in the last year?
A. I think more than a year.
Q. More than two years?
A. I don't think so. I would say if that's my -- if that's the time -- the choice, I would say probably in one to two years.
Q. Who first contacted you about this case?
A. I don't know who actually sent me

the first email, but I ended up talking to a Ms. Dana Weir.

Q. Were you first contacted about this case via email?

A. I'm pretty sure at least the initial contact. I mean, I ended up pretty soon thereafter having a Zoom call or something like that to discuss issues or whatever. You know, whatever, if I was suitable or whatever they needed.

Q. And what was your first impression on hearing about this case for the first time?

A. By "impression," what do you mean?

Q. What did you think about this case when you heard about it for the first time?

A. I didn't have an impression. I mean, my impression of my -- the issue for me was did I have the wherewithal and expertise to be able to competently and effectively fulfill the role that the law firm needed in dealing with this.

My second thought was patent case. Who the hell understands patent law anyway. It's all totally off the wall, and I'll never understand what's going on here, and after I

dealt with those two issues, then it was pretty straightforward.

Q. When did you start working on your declaration for this case?

A. That would be -- it depends on what you mean by "working on." I mean, I started early on reading various documents that were germane to the case, so that took place from early after coming in contact or after signing on as an expert in the case. So I would include that as part of the preparation of the declaration.

So that -- let's assume for the moment that this all took shape two years ago, which is possible, it's probably a little less than that, but if we talk about the actual preparation of the written document, I'm going to guess or believe that that was -- if I signed this in November, then the preparation of the declaration would have been early in the fall. So that would have been not a year ago, but a little less than a year ago.

Q. And once you started preparing your declaration, how much time did you spend on it?

A. I can't -- I can't estimate the hours.

Q. Do you have a ballpark estimate of the hours you spent on the declaration?

A. Again, if we include the reading of the documents and things of that sort, then we're talking -- and the various meetings with the lawyers, then we're talking 50 to 75 hours.

Q. In preparing your declaration for this case, did you look for articles that expressed a view contrary to yours?

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

A. As I said before, the lawyers obtained the articles for me. I did not personally do a literature search on the subject, but I am not sure what a negative article would have said. Would it have said that MSI high colorectal cancer is not treated by immunotherapy? I suppose there are some articles that do say that, but -- and then I don't know that that is an important -- in its context that that's really an important

1 counterargument here. We're not really
2 arguing about whether immunotherapy is -- or
3 at least I'm not arguing about whether
4 immunotherapy is effective in MSI high
5 colorectal cancer. So I'm not looking to
6 rebut that.
7 I did not look for articles that
8 looked at the role of Hopkins versus the role
9 of Merck, if that's what you're referring to.
10 And so -- and I did not look into the
11 legalities of the issue because that's not my
12 role and not my expertise.
13 So again, I don't know what -- if
14 you say did I look for articles that were
15 negative or opposed the views of these
16 articles, I don't know what -- did I look for
17 an article that said you don't give
18 pembrolizumab intravenously? No, that would
19 have been silly, but so there was no counter
20 to these articles in my -- to look for.
21 Q. In preparing your declaration for
22 this case, did you look for articles that
23 discussed the importance of Hopkins'
24 contributions to cancer treatment by
25 demonstrating the efficacy of treating MSI

high cancer patients with pembrolizumab?

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

A. As I said, I did not address the relative contributions of Hopkins versus Merck or the -- if you'd like, the actual nitty-gritty of the various litigation claims that are either in the district litigation or in the District Court litigation or in the patent litigation, except insofar as they're addressed in the declaration with regard to the obviousness or anticipation of the patent itself.

Q. Are you aware that there are articles discussing the importance of Hopkins' contribution to cancer treatment by demonstrating the efficacy of treating MSI high cancer patients?

ATTORNEY RATLIFF: Are you representing that to be true?

(No response.)

ATTORNEY RATLIFF: Okay. If you're not going to answer my question, I object to the form of your question, as well as to the

premise of your question.

A. I imagine there are articles that give the story one way or the other, but I don't know one way or the other what it is, and it's not my job and it's not my role and I don't really care one way or the other what they would say.

Again, my only claim here is that the MSI high study record has all the information in it that's ultimately addressed in the claim. So they're reported in the patent, and that again, a POSA would have seen that and it would have been anticipated or obvious prior to the patent and that the patent board should be aware of that, etc.

Q. Do you teach oncology medical students?

A. I used -- if you're saying directly to medical students, I used to participate in the second-year medical student course. I haven't done that in a while. To be honest, I'm above that, but I do teach third-year students -- well, okay, they're students too, and I mostly teach on the fellow level. I teach fellows.

Q. Do you teach oncology fellows to treat MSI high cancer with pembrolizumab?

A. I use the term "immunotherapy," yes, including pembrolizumab.

Q. And what was the process like for creating your declaration? And I don't want to know any conversations between you and your attorneys in doing this, but just the mechanics of how it worked?

A. As I said, I had long preliminary discussions with the various attorneys. I read various documents and exhibits that are included in the list of exhibits and so that I understood all those issues involved, as well as the MSI high study record itself and the patent, etc., and the claims. I was sort of educated about the patent law process enough so I could appreciate what a POSA was and those sorts of patent law issues, at least on a pretty decent level, so I was not totally out of the loop and being able to think about such things.

Ultimately, I discussed these issues and the key points that are in the declaration with the attorneys. I, myself,

did not actually write the initial document. That was written by the attorneys and a draft was given to me. I went over it very carefully and made significant amendments that went back and forth for a while and then came up with the final document.

Q. In forming your opinions for this case that are reflected in your declaration, did you consult with anyone other than the lawyers?

A. I did speak to my wife. She did not understand one word -- she's a lawyer, but she did not understand one word of the patent law issues. So I gave that up and she wished me the best of luck, but aside from that, I haven't spoken to anyone about it.

Q. In paragraph 16 of your declaration, you state that you were asked to assume that the relevant time period could also be November 13, 2014, but none of your opinions would change in view of that date, and if you want to get to it, let me know when you're there.

A. Yeah, give me a second.

Q. Sure.

Paragraph 16.
A. Uh-huh. I'm sorry, what's your question?
Q. So in paragraph 16 of your declaration, you state that you were asked to assume that the relevant time period could also be November 13, 2014, but none of your opinions would change in view of that date; is that correct?
A. Yes.
Q. What did you do to assess whether your opinions would change in light of the November 2014 date versus the July 2015 date?
A. What was I asked to do if -- what did I do to consider November 13, 2014?
Q. I'm asking specifically about that phrase in your paragraph 16.
A. Right. I understand.
Q. And what did you do to assess whether your opinions would change in light of the November 2014 date versus the July 2015 date?
A. I didn't do anything.
Q. Dr. Neugut, have you served as an expert in any capacity for Merck other than

for this dispute?

A. I've -- I've consulted for Merck in the past in unrelated circumstances. So it would not be relevant to anything we're talking about today.

Q. I'll come to the consulting in a minute, but have you served as an expert for Merck other than for this litigation?

A. I don't believe so.

Q. You said you've done consulting for Merck unrelated to what we're talking about here. When was that?

A. I don't recall exactly. I do pharmacoepidemiology consulting. So I consulted for Merck in the past on issues related to their drugs and their clinical trials.

Right now I serve on a DSMB for drugs, for certain diabetes drugs which are being evaluated, which are being monitored, and, again, it has nothing to do with anything, but I think it involves several drug companies that have diabetes drugs of a certain class, and I think one of the companies was Merck, but again, it has nothing

to do with anything we're talking about today, but if you're asking, I'm telling.

Q. Have you collaborated with any research -- on any research projects with Merck?

A. Not to my -- not to my recollection. The former CEO of Merck hangs out at Columbia a lot. So I've been to dinner with him a couple of times, but I don't think that counts as anything.

Q. Who is that former CEO of Merck you're referring to?

A. His name is Vagelos.

THE WITNESS: Vagelos, V-A-G-E-L-O-S.

Q. Have you worked with Merck's counsel before, which is Paul Hastings?

A. No.

Q. I asked you a few questions ago about your work relating to this litigation. Is it your understanding that this litigation includes the District Court litigation or just the dispute in front of the Patent Office?

A. The one we're discussing today is distinct from the District Court litigation, and I understood that that litigation was

suspended or I don't know what word is used legally, but it's in abeyance until this patent issue is resolved.

Q. Have you ever consulted for Johns Hopkins?

A. I don't recall consulting for them.

Q. Have you ever worked with any researchers from Johns Hopkins?

A. I'm sure that I have, but as I sit here, I don't recall any.

Q. Do you consider Johns Hopkins to be a good research university?

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

A. Yes.

Q. How much have you been paid for your work in connection with this case?

A. I get 650 an hour.

Q. And do you know how much you have earned to date for your work on this case?

A. As I'm sitting here, I don't know offhand, but I'm going to guess in the ballpark of or estimate in the ballpark of $40,000.

Q. You've served as an expert witness

in a litigation before; right?
A. In a litigation?
Q. (Indicating.)
A. I do a fair amount of litigation consulting.
Q. And are you aware if any of your testimony has been excluded as part of your work doing litigation consulting?
A. Am I aware if any of my --
Q. Testimony has been excluded?
A. Once, uh-huh.
Q. When was that?
A. I'm not sure exactly legally what it was, but it was around 2017.
Q. And why was your testimony excluded?
A. To be honest, I'm not exactly sure what the legal basis was. I think it was a misunderstanding by the judge, but there is a big -- there is a big litigation or a big -- there is a lot of litigation going on with regard to an herbicide called Roundup going on. So I was the -- or I am one of the main plaintiff witnesses with regard to the relationship between Roundup and non-Hodgkin's

lymphoma.

So when the case was initially in litigation, there was, I think what you call, an MDL, I don't know what the letters stand for, but so there was a Daubert hearing on the subject, and the judge who heard the case, this was in some Federal Court in California -- I mean, the testimony went on for hours and the judge said I contradicted myself in the testimony. I was asked a few times the same question back and forth. It was on technical points, but I didn't. I mean, he didn't understand it. The truth is there were two different answers to the same question, but whatever. So he said because I contradicted myself that -- or this is how I understood what happened, that my testimony wasn't reliable, and he excluded me from testifying further in, I guess, some federal cases with regard to Roundup.

Q. How many cases have you been an expert witness for?

A. I testify a lot. I would have trouble quantifying that. I probably -- I don't testify very much, but I review a lot of

cases.

Q. How much time would you say you spend serving as an expert witness for litigations?

A. Well, I have two aspects to my litigation consulting. I do malpractice reviews and I do mass tort reviews, because, again, I'm an epidemiologist, so I do a lot of, you know, drug epidemiology. I testify against drug companies. So -- or whoever, so I would say I do about -- I do one to two malpractice cases a month to review, but again, they never -- they hardly go to court. They all settle or they have no basis, so they review them and that's the end of the case.

In the mass tort area, I do, I don't know, two or three cases a year. Again, Roundup has been like the big -- a big thing for me because that seems to go on forever. It's a case of all time, but I haven't had that many. You know, maybe I do two Roundups a year or I've been doing two Roundups a year since 2017, but always in state court. And then I've had a couple of -- a few other mass tort cases. So that's been that.

Q. And have you served as an expert witness in a patent case before?
A. Once.
Q. What case was that?
A. There was a case against Genentech. I was on the plaintiff -- I was the expert witness on the plaintiff side. It was for a drug called Avastin, also a colon cancer -- a very commonly used colon cancer drug. The issue there was that Genentech had a long-standing patent on the drug, and the plaintiff was a company -- a generic company that wanted to, I guess, make the drug and wanted to -- I don't know what you'd call it, wanted to get around the patent and then have permission to make the drug or to be able to produce it and stop the patent and argue that whatever the basis was, Genentech had for lengthening out, they kept lengthening out the patent, whatever the argument they were making for lengthening the patent another two or three years or however they were doing it, but the basis for the patent extension was not legitimate.
Q. So in that Genentech patent

litigation, you served as an expert witness for Genentech?

A. For the generic firm.

Q. Have you been engaged by Merck as an expert for the District Court litigation against Hopkins?

A. Not to my knowledge.

Q. And I would hope you would know.

A. Huh?

Q. I would hope you would know if you've been engaged.

All right.

Dr. Neugut, what did you do to prepare to give testimony today?

A. I have met with the attorneys multiple times and I have reread all these documents and I have reread my declaration any number of times and I got a good night's sleep.

Q. When you say you met with the attorneys to prepare to give testimony today, how many times did you meet?

A. The meetings varied in length and intensity, but if you add them all up, I would say seven or eight times.

Q. And I want to make sure that you understand I'm just talking about preparing for the deposition, not also your declaration. Is that your understanding?

A. Yes.

Q. Okay. So you met seven or eight times to prepare to give testimony today; right?

A. But as I say, some of the meetings were an hour or two.

Q. And who did you meet with?

A. The occasions varied and the granatis personi varied from meeting to meeting and depending on the occasion involved Mr. Ratliff, Mr. Feigenbaum, Daniel, whose last name I can't remember as I'm sitting here. Ms. Moreira, that Dana Weir, who is not here. Another Merck attorney whose name I also cannot recall, and there was someone else I'm not remembering.

Q. And during those seven to eight meetings with attorneys that have varying lengths, did you review any documents?

ATTORNEY RATLIFF: Doctor, I instruct you not to answer that question.

ATTORNEY KRANING: He can't.

ATTORNEY McCORMICK: He can't answer a yes-or-no question about whether he reviewed documents?

ATTORNEY RATLIFF: One, you didn't say it's a yes-or-no question. Two, I don't believe there is such thing as a yes-or-no question. Three, it seems like you're seeking privileged information.

(Direction not to answer the question.)

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, if you can answer yes or no, please, as part of the meetings to prepare for your testimony today, did you review any documents?

A. I don't want to answer based on Mr. Ratliff saying I shouldn't answer.

Q. Dr. Neugut, if we get the chance to depose you again, do you have any general objection to being videotaped?

ATTORNEY RATLIFF: I object to the form of the question, and, Doctor, I instruct you not to answer that question.

(Direction not to answer the

question.)

ATTORNEY McCORMICK: On what basis?

ATTORNEY RATLIFF: On a privilege basis.

ATTORNEY McCORMICK: It's privileged whether he's okay being videotaped?

ATTORNEY RATLIFF: Yeah. Counsel, you're rolling your eyes?

ATTORNEY McCORMICK: I did not roll my eyes, Preston.

ATTORNEY RATLIFF: Counsel, I'm looking directly at you, that's what you're doing.

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, are you going to follow Mr. Ratliff's instruction not to answer my question about not being videotaped?

A. Of course.

Q. All right.

ATTORNEY McCORMICK: If we can just take a short break, I think we can be done.

We can go off the record.

CERTIFIED STENOGRAPHER: Off the stenographic record at 3:18 p.m.

(Whereupon, a recess is taken.)

CERTIFIED STENOGRAPHER: Back on the

stenographic record at 3:30 p.m.

BY ATTORNEY McCORMICK:

Q. Dr. Neugut, did you discuss the substance of your testimony with counsel during the break?

A. No.

ATTORNEY McCORMICK: Dr. Neugut, I have no further questions for you today. Thank you very much.

ATTORNEY RATLIFF: And, Dr. Neugut, on behalf of the petitioner here, I have no questions for you. We're done.

ATTORNEY McCORMICK: We can go off the record.

CERTIFIED STENOGRAPHER: Off the stenographic record at 3:30 p.m.

(Time noted: 3:31 p.m.)

_____

ALFRED I. NEUGUT, M.D., Ph.D., MPH

I wish to make the following changes, for the following reasons:

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C E R T I F I C A T E

I, RICHARD GERMOSEN, Fellow of the Academy of Professional Reporters, stenographic New Jersey Certified Court Reporter, New Jersey Certified Realtime Court Reporter, California Certified Shorthand Reporter, California Certified Realtime Reporter, NCRA Registered Diplomate Reporter, and NCRA Certified Realtime Reporter, do hereby certify:

That ALFRED I. NEUGUT, M.D., Ph.D., MPH, the witness whose deposition is hereinbefore set forth, having been duly sworn, and that such deposition is a true record of the testimony of said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of August 2024.

RICHARD GERMOSEN,
FAPR, RDR, CRR, CCR-NJ, CRCR, CSR-CA, CCRR-CA, NYACR, NYRCR
LICENSE NO. 30XI00184700
LICENSE NO. 30XR00016800
California CSR No. 14391
California CRR No. 198

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