UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case No. IPR2016-003181

U.S. Patent 7,772,209

- -

SANDOZ INC., APOTEX INC., APOTEX CORP.,
EMCURE PHARMACEUTICALS LTD.,
HERITAGE PHARMA LABS INC.,
HERITAGE PHARMACEUTICALS INC.,
GLENMARK PHARMACEUTICALS, INC., USA,
GLENMARK HOLDING SA, GLENMARK PHARMACEUTICALS,
LTD., MYLAN LABORATORIES LIMITED,
TEVA PHARMACEUTICALS USA, INC. and
FRESENIUS KABI USA, LLC,

Petitioners

v.

ELI LILLY AND COMPANY,

Patent Owner.

- -

VIDEOTAPED DEPOSITION OF BRUCE A. CHABNER, M.D.

Thursday, November 10, 2016 8:16 a.m.

Foley Hoag LLP

155 Seaport Boulevard, Boston, MA

Reporter: Janet M. Sambataro, RMR, CRR, CLR

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I N D E X

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P R O C E E D I N G S

THE VIDEOGRAPHER: Here begins the videotape No. 1 in the deposition of Bruce A. Chabner, M.D., in the matter of Sandoz versus Eli Lilly. In the U.S. Patent and Trademark office before the patent trial appeals board, Case No. IPR2016-00240 [sic].

The date today is November 10, 2016, and the time is 8:16 a.m. The video operator today is Steven Baty. This video deposition is taking place at Foley Hoag, 155 Seaport Boulevard, Boston, Massachusetts.

Counsel please voice identify yourselves and state whom you represent.

MR. GROSSMAN: This is Dov Grossman of Williams & Connolly, on behalf of patent owner, Eli Lilly.

And, just to clarify, this is in IPR2016-00318.

THE VIDEOGRAPHER: Oh. I had the wrong information. 00?

MR. GROSSMAN: 318.

THE VIDEOGRAPHER: 318. Thank you.

MR. SKIERMONT: Paul Skiermont. I'm representing Neptune Generics, LLC.

MR. GABRIC: We'll just go around the room.

THE VIDEOGRAPHER: We'll go around the room.

MS. MALMBERG: Mieke Malmberg of Skiermont Derby, also for Neptune.

MS. SPIRES: Sarah Spires of Skiermont Derby, also for Neptune.

MR. KILGORE: Patrick Kilgore for Apotex.

MR. NAGGAR: Charles Naggar of Alston & Bird for Mylan.

MR. PARKER: Tom Parker, Alston & Bird, for Mylan defendants.

MS. LYDIGSEN: Laura Lydigsen from Brinks Gilson & Lione for Sandoz, Inc. And on the phone we have Michael Cottler from Goodwin Procter for Fresenius.

MR. GABRIC: Good morning. Ralph Gabric from Brinks Hofer, on behalf of Sandoz, Inc.

THE VIDEOGRAPHER: The court reporter -- oh, one more.

MR. PATARIU: And David Patariu, Pillsbury Winthrop Shaw Pittman, for Wockhardt

Bio AG.

THE VIDEOGRAPHER: Thank you. The court reporter today is Janet Sambataro of DTI.

Would you please swear in the witness.

BRUCE CHABNER, M.D.,

having been duly sworn, after presenting identification in the form of a driver's license, deposes and says as follows:

CROSS-EXAMINATION

BY MR. GABRIC:

Q. Good morning, Dr. Chabner.

A. Hi.

Q. You've had your deposition taken before. Correct?

A. Yes.

Q. All right. And you are familiar with the ground rules. I get to ask some questions and --

A. I get to answer.

Q. Correct.

A. Yeah.

Q. Any reason why you are compromised in your ability to testify today?

A. A husky voice.

Q. But you're not on any medication that

would affect your ability to testify?

A. No.

Q. Nothing else that would affect your ability to testify?

A. No. Only my intelligence.

Q. Okay. Well, you've got plenty of that, as far as I can tell.

A. Hopefully.

Q. All right.

A. Tell me your first name.

Q. I'm sorry. My first name is Ralph.

A. Ralph.

(Lilly Exhibit 2120 incorporated by reference.)

BY MR. GABRIC:

Q. I'm going to show you what has been marked as Exhibit 2120 in this matter and ask you if that's a declaration you prepared for this matter?

A. It does look like it. I haven't looked at every page of it. I won't, but it does look like it, yes.

Q. All right. And have you reviewed that declaration since it was prepared?

A. I have.

Q. Okay. And did you find any errors in it or anything like that?

A. Yes. Some spelling errors and some -- there are some errors in it. Yes.

Q. How about substantive errors?

A. Not really. I mean, there was one place where the creatinine, instead -- it was creatinine clearance instead of creatinine and serum creatinine, which makes a difference, to me at least, but it's just an error.

Q. Okay. Where in that declaration?

A. I don't know. I can't tell you. I don't have the page number.

Q. Okay.

A. If we get to it, I'll show it to you.

Q. All right.

A. And there are several other spelling errors and things. Yes.

(Lilly Exhibit 2121 incorporated by reference.)

BY MR. GABRIC:

Q. I'm going to show you Lilly Exhibit 2121. Do you recognize that document?

A. That's -- yes.

Q. That's -- is that a current copy of

your CV?

A. It's a copy as of last year.

MR. GROSSMAN: Do you have a copy for Counsel?

MR. GABRIC: Oh, I'm sorry.

Q. Anything significant to add to your CV since last year that we should be aware of, as far as you're concerned?

A. Yeah. A number of papers and a -- maybe a significant honor. Yeah.

Q. Any of those papers on pemetrexed?

A. Oh, that's go- -- an interesting question. Probably not. Probably relative to some of the issues, but not on pemetrexed.

Q. What issues would those papers be relevant to from your perspective?

A. Approval process for new drugs. The FDA. And one important paper, I think, on -- on how to screen for antitumor activity using cell lines.

Q. Any other papers?

A. Yeah. A couple of others, but not relevant to this, I think.

Q. Now, judging from your CV, you worked previously at the National Cancer Institute, NCI?

A. That's right.

Q. For about 20 years?

A. Almost 27 years.

Q. And the NCI, is that part of the National Institute of Health?

A. It's part of the National Institutes of Health. It's one of the institutes.

Q. And at the NCI, just generally, what did your duties involve?

A. Well, I came there, first, for training in medical oncology and then a period of research in drug development and pharmacology. And after spending two years away, one year in the junior faculty at Yale in the pharmacology department, I came back there as an attending in the medical oncology group, but also as a laboratory person studying anticancer drugs and I became the laboratory chief of clinical pharmacology and then the head of the intermural clinical service, director of the clinical oncology program.

And then in 1981, I was appointed as the head of the division of cancer treatment, in an acting role, and then shortly afterward became the permanent director. And in that capacity, I was responsible for the national program for

cancer drug development and cancer drug discovery, the programs that the Federal Government sponsored. And the clinical trials network outside, plus intermural research. And I continued in that job for 13 years until 1995. And then I was in the Public Health Service at that time.

Q. Now, in the period leading up to June of the 1999 time frame, what role, if any, did the NIH have in setting standards for clinical trials?

A. Well, it was the major force in sponsoring clinical trials, working with industry, both in cancer and AIDS. We were responsible, we were really the sole drug development program in the -- in the Federal Government for cancer, and then later for AIDS, drug discovery, drug development. And then we ran the clinical trial system that -- that tested these compounds that we came up with.

Q. And what is the clinical trial system?

A. Well, it was cooperative group system, and the intermural research system at the NIH, which was quite large. And 25,000 patients on trial a year, through that federal system.

Q. I want to jump in a time machine and go back to June of 1999 time frame.

A. Yeah.

Q. Were clinical trials segregated into phases?

A. Yes. Certainly. So there were the typical drug went through three phases of testing and we were responsible, we had contracts for the first Phase 1 and Phase 2 trials. And then Phase 3s were usually done in the cooperative groups, which were also one of our responsibilities.

Q. And you used the terms Phase 1, Phase 2, and I believe Phase 3. Correct?

A. Right.

Q. What is a Phase 1 trial, as of June of 1999 time frame?

A. Well, the -- Phase 1 trial was the first initial trial of a drug that goes into the clinic, where we're trying to determine what is the appropriate dose and schedule and whether there's any early evidence of clinical activity. And there are a number of studies that are done in conjunction with that. 1999 was a transition time when different sorts of drugs were coming

into the clinic, so they were called targeted drugs. And with those drugs, there was a somewhat different approach to the Phase 1 trial, where biomarkers were used and patients were highly selected to go into that -- that trial. And probably, I guess in the mid '90s, were putting maybe four or five drugs into Phase 1, coming from our program and there were some from industry that came through our program.

Q. And what would be the primary objectives of the Phase 1?

A. Well, as I said, to establish a safe and effective route of administration and to do pharmacokinetic studies and to look at evidence of clinical activity and toxicity.

Q. And when you say "clinical activity," what are you referring to?

A. Tumor responses.

Q. Efficacy?

A. No. Tumor responses.

Q. Okay. Is that efficacy in --

A. Well, that's what you're trying to do.

Q. And it's your testimony that that's one of the primary objectives of Phase 1 in the June of 1999 time frame?

A. Yes. Certainly it's one of the objectives. Whenever you give a drug to a cancer patient, you're hoping that the patient gets better. I mean, we wouldn't just give a drug because we were interested in what happened to the drug without knowing what happened to the patient.

Q. Yeah. I under- -- I understand what you're hoping for. My question is a little different, though, Doctor.

Is it your testimony that a primary objective in a Phase 1 study, in June of 1999, was to evaluate --

A. It's always that --

Q. -- efficacy?

A. -- in a clinical trial. You know, the first time you put a drug into the patient, you do a lot of other things, certainly. And you want to certainly establish the regimen that you're going to use is safe. And it gives you drug levels that are going to be, you hope will be effective. You're extrapolating from animal studies, but you're also watching what happens to the patient and the tumor. And there was a certain degree, at that time, of tumor selection

went into the Phase 1 trials, based on what we knew about the drug in the preclinical experience. These are therapeutic trials.

(Printout from ClinicalTrials.gov marked Exhibit 1063.)

BY MR. GABRIC:

Q. Doctor, I'm going to show you Exhibit -- what we've marked as Exhibit 1063.

A. Yes.

Q. And I'll represent to you for the record that this is a printout from the Wayback Machine website from January of 2001, a couple of years after June of 1999. I'll give you a chance to look at that. And I want to focus on --

MR. GROSSMAN: Counsel, before you show him this exhibit, I'm going to object. You haven't established this as prior art. And under the rules you need to cure that objection.

MR. GABRIC: I'm not representing this is prior art. I'm using this to -- I don't have to give any explanation, but I don't have to prove this is prior art to use this with this witness. I believe this document is inconsistent with the witness's testimony. That's why I'm showing it to him.

MR. GROSSMAN: Well, I'm going to object, based on your representation, A, it's not prior art. B, you have no documentation from the Wayback Machine, such as a declaration accompanying this showing that this is from the time period you say it is, which is not prior art.

MR. GABRIC: Your objection is noted, Counsel.

Q. This is a -- are you familiar with the Wayback Machine?

A. No, I'm not.

Q. Okay. It's a service that goes back and captures website -- pages, website pages that existed at certain time frames. And we went back and captured a website page from the National Institute of Health. Okay? And --

A. This is --

Q. -- they discuss here Phase 1 trials. Do you see that?

A. Yes.

Q. All right. And can you read into the record what it says with respect to Phase 1 trials?

A. "Clinical trials in which researchers

testing new drug or treatment -- treatment in a small group of patients or people for the first time to evaluate safety, determine a safe dosage range, and identify side effects."

Q. Right. So on this -- on its website, the NIH is basically saying the purpose of a Phase 1 clinical trial is to, "evaluate its safety." Right?

MR. GROSSMAN: Objection.

A. It doesn't say "purpose." It says proceed through phases. It doesn't say purpose.

Q. Okay. Do you see where it says "in Phase 1 clinical trials." Correct?

A. I do.

Q. All right. And it says "evaluate." Do you see that?

A. Yes.

Q. Okay. And, "Evaluate its safety," the drug's safety. Correct?

A. Right. That's what I said.

Q. Okay. Then it says "determine a safe dosage range." Do you see that?

A. Right.

Q. And it says, "identify side effects," right? Do you see that?

A. Right.

Q. It doesn't say "identify efficacy," does it?

A. It says --

MR. GROSSMAN: Objection.

A. -- treatment, doesn't it?

Q. So is it your testimony --

A. What is a treatment?

Q. I want to make sure I understand your testimony.

So your testimony is, is the statement here "treatment" means evaluate evidence?

A. So you always want to get a look at what it does to the tumor. I mean, you don't think people take x-rays when they're doing this? They don't do physical exams on patients while they're getting it? That's a very important part of it. It's a treatment experiment.

Q. Okay. So it's -- your testimony that a primary objective of a Phase 1 trial is --

A. One of the objectives. Yes.

MR. GROSSMAN: Dr. Chabner, it might be easier if you let Mr. Gabric finish his question before preceding with your answer.

THE WITNESS: Okay.

MR. GROSSMAN: Plus give me time to object, if necessary.

THE WITNESS: Oh, okay.

BY MR. GABRIC:

Q. Now you see now the entry for Phase 2 clinical trials?

A. I do.

Q. Okay. And here they say, "the studied drug or treatment is given to larger group of people to see if it is effective and to further evaluate safety." Right?

A. Yes. That's right.

Q. All right. So Phase 2, the NIH uses the term to see if it's effective. Right?

A. And that's because you have a larger group of patients, so you get some statistical idea or more solid statistical idea.

By the way, this is a rather brief description of Phase 1 trials. What happens after a Phase 1 is we can go back and do Phase 1b trials, which try other regimens or changes in the regimen that we've established for Phase 1. And a Phase 1b does have different connotations.

Q. I'll get to Phase 1b in a second. Thank you, Doctor.

You said this was kind of a brief summary. Is it inaccurate?

A. It's -- it's not complete.

Q. Is it inaccurate? Do you disagree?

A. I didn't say --

MR. GROSSMAN: Objection. Asked and answered.

A. I didn't say it was inaccurate in what it says, but it's incomplete.

Q. So it's your testimony that the NIH has incomplete discussion of Phase 1 and Phase 2 trials here?

A. Well, this is a very brief thing. I don't know who wrote this, I have no idea who wrote this. It wasn't -- I certainly didn't write it.

I would say this: That when you give a drug to a patient, whether it's experimental or not, an anticancer drug, you're always interested in whether it has antitumor efficacy. That's one of the -- I mean, it would be unethical to give it otherwise.

Q. You used the term "Phase 1b."

A. Yes.

Q. Okay. I don't see the Phase 1b trial

listed on this Exhibit 63 [sic]. Is that a term that was used in June of 1999?

A. Absolutely.

Q. Absolutely?

A. Yes.

Q. By who?

A. By all of us.

Q. What is a Phase B1 -- Phase 1b trial?

A. 1b.

Q. What is that?

A. It's a -- it's a derivative trial, in which you change the schedule. You may focus the trial on a specific subset of patients, but it's not the first Phase 1.

So a Phase 1, the first time you put it into patients, that's Phase 1. You're mostly interested in safety and pharmacokinetics and you're also looking at -- at whether you get a tumor response when you get to a dose that you think is -- is reasonable.

A number of trials will follow if you want to change the regimen. So let's say I want to give intermittent dosing rather than a single large bolus, daily times five, or a -- another regimen, and it could be, you know, a significant

variation. But it builds on what you've learned from the Phase 1 trial. And that's called a Phase 1b trial.

And those, in fact, can lead to drug approval. There are many examples now of drugs that go through a very shortened development phase because suddenly we understand who to give the drug to. And it's called Phase 1b and then it leads into an early Phase 2 or you may not need the Phase 2.

Q. As you sit here today, can you identify any publication, pre-June of 1999, that defines or refers to what you are calling a Phase 1b trial?

A. I'm -- I'm certain I can find the protocols which describe Phase 1b trials. Yes.

Q. Is there anything in your declaration, any of those papers cite those protocols?

A. I -- I don't remember. I don't know if the issue came up.

Q. And was -- as of June of 1999, was there any definition of Phase 1b trials --

A. Oh, I'm sure.

Q. -- on the NIH website?

A. Well, I don't know. I can't tell you.

You know, that's a rather large question, isn't it? I don't know.

Q. Is that a term that the NIH used?

A. Yes. I used it.

Q. You used it.

A. All my people, all people that worked for me used it.

Q. Was that a formal definition that the NIH used?

A. I was the person that set the standard, I guess.

MR. GROSSMAN: Counsel, just -- just for the record, you're required at a deposition when you introduce a document like this to cure any objections. I've objected to it for the grounds I stated earlier. You didn't cure it, so we reserve the right to strike -- to strike all testimony concerning the document.

BY MR. GABRIC:

Q. So could you summarize your expertise with antifolates?

A. Yes. In 1969 I went to -- into the laboratory at Yale, worked with a Dr. Joseph Bertino, who was one of the leading people in terms of understanding the mechanism of action of

antifolates and methotrexate, which is one of the first antifolates. And I worked on a project to develop a bacterial enzyme that would cleave folates and would produce folate deficiency. And we did it, we took a Pseudomonas enzyme, purified it, worked with the people to New England Enzyme Center to produce large quantities of the enzyme and then actually gave it to patients. It was one of the first -- I think it may have been the first example of an exogenous enzyme given to a human for treating a -- a disease.

The people I worked with went on to found Genzyme, which is -- I was sad to see them leave the project. The drug actually proved to be useful in dealing with methotrexate toxicity, because it cleaves folates. And it's now approved for clinical use for that use.

Q. Methotrexate?

A. No. The enzyme.

Q. The enzyme?

A. Yes. It's called glucarpidase. And after that, I went to NIH. I was working on that specific project at NIH. But I worked on a lot of other projects related to antifolates, including pharmacokinetics, high-dose

pharmacokinetics and how it related to the toxicity we were seeing with high-dose methotrexate.

I developed a monitoring system that was used to follow patients and to predict toxicity. We discovered the mechanism of renal damage related to methotrexate and developed a regimen of alkalinization and hydration that prevented that -- that toxicity. It's a rather complicated regimen, and the toxicity was overwhelming in some patients. And so it was a very useful measure.

We also studied the interac- -- the interrelationship of methotrexate and reduced folates that were used for rescue and established the principle that this was a reciprocal -- not a reciprocal, but a competitive relationship.

We studied the process of polyglutamation of antifolates and showed that the polyglutamation led to enhancement of activity against thymidylate synthase and some of the other purine enzymes.

And we conducted some studies with antifolates in people, one of which led to the approval of a new antifolate for treating

pneumocystis pneumonia, which was occurring in AIDS patients. And that's -- that's pretty much the summary.

Q. Thank you, Doctor.

So is it fair to say that the bulk of your hands-on research activity was with respect to methotrexate?

A. Most of it, yes.

Q. And --

A. There were a few other antifolates that were -- we were interested in?

Q. Did you do any hands-on research on pemetrexed?

A. Hands-on, no.

Q. And if I understand your testimony correctly, your work on methotrexate, that was pre-June of 1999?

A. Well, the laboratory work was certainly prior to 1999. It was 1999 and below -- and prior to that. It was probably mostly 1995 and -- and earlier.

Q. And is it fair to say that toxicity was a concern with respect to methotrexate?

A. Oh, it's always a concern with all the cancer drugs. We were fortunate that, because we

understood a good deal about it and had ways of using antidotes and the enzyme that I described, that we could -- we could actually manipulate methotrexate much better than some of the other drugs that we were working with.

Q. And so as of June of 1999, toxicity was also a concern with respect to pemetrexed as well?

A. Yes, it was. Yeah. But it was -- pemetrexed was mainly in the hands of Lilly at that time, not with the NCI.

Q. Now, I'm looking at your CV.

Let me back up for a second. While you were doing your work on methotrexate, it sounds like you have a fair amount of research experience in that area.

A. I would say so, yes.

Q. All right. And did you make it your practice to stay abreast of the relevant publications in that area?

A. I tried.

Q. It would be important to keep abreast of the important publications in that area so that you knew what was going on with respect to methotrexate. Right?

A. Yes. And I had a more general interest in this because I was writing textbooks.

Q. Okay. So did you make an effort to monitor the publications in the area of methotrexate prior to June of 1999?

A. Well, of course. Yes.

Q. Now, you have a heck of a lot of publications listed on your CV.

A. Most of --

Q. Seventy or so.

A. Most of them are authentic, yes.

Q. And so is it fair to say, I'm not going to ask you to count them all, but I mean, ballpark, you have about 200 peer-reviewed publications --

A. Well --

Q. -- does that sound about right?

A. It's -- it's not really complete in the sense that the system in the university where I am segregates publications into chapters, books, editorials and so forth so that they don't all count. But there are probably, you know, in the 200s in terms of peer-reviewed publications in journals, yes. Those are the ones that the university cares about, because when they look at

you for promotion, that's where they really look.

Q. Publish or perish, I think is the term?

A. Publish in peer-reviewed journals, yes. I haven't perished.

Q. No, you haven't, thankfully.

Now, do you have -- currently have an active practice?

A. I have -- my primary role is clinical research, mentoring young faculty, attending patient conferences and helping in making decisions about patients through conferences, and then a brief period of attending during the year in the medical service at Mass. General. I'm a medical attending on the inpatient service there. Yes. And maybe of all the things I do, I enjoy that the most.

Q. And if it's varied, you can let me know, but in the last five years, about what percentage of your time is devoted to actually treating patients?

A. Okay. In the last five years, the number of patients I've followed at the clinic has diminished. We're all getting older, unfortunately some of them are succumbing to other illnesses. And so at the moment I have

very few patients I follow in the outpatient clinic.

Probably, I would say that my clinical activities and involvement account for something like 5 to 10 percent of my -- my time. I still get a lot of referral of patients asking for consultation about management questions, particularly with lymphoma patients and some with breast cancer. But the bulk of my activity is in writing and mentoring and clinical research.

Q. When is the last time -- let me ask you this: Have you ever prescribed pemetrexed?

A. I've supervised the prescription of pemetrexed through the lung cancer program. I'm not a lung cancer doctor, so I wouldn't prescribe it myself.

There's another area where I have been involved and that is in the CNS lymphomas, where we had an active protocol looking at the activity of pemetrexed and I was part of that.

I -- I actually didn't manage those patients directly, I collaborated with the neuro-oncology service. But there were -- there were many patients. When I was the clinical director of the cancer center, which was until 2000- -- I

think 2011, I did supervise the whole service, and that was a very active part of it.

I would say that I'm very familiar with the clinical use of it and the side effects and the benefits that have come from it.

Q. Have you, yourself, ever prescribed it?

MR. GROSSMAN: Objection to the form of the question.

A. Have I ever prescribed it personally?

Well, number one, I don't prescribe drugs on the medical service when I'm attending. Two, I follow lymphoma patients. So the only lymphoma patients who have been treated with pemetrexed were on the protocol which I described, and I did not write the prescription. The prescriptions are, in general, written by junior staff or fellows.

Q. And the last five years, how many patients have you followed who have been on pemetrexed?

A. I follow a number of people through consultation. I don't take care of them on a daily basis. So -- but it's a small number.

Q. Can you ballpark "small" for me?

A. Maybe five.

Q. Around five in the last five years?

A. Yeah.

Q. Now, we were talking a little bit about Phase 1, Phase 2, Phase 3 trials. I think there's a Phase 4. Right?

A. Post-marketing.

Q. Post-marketing.

What phase is efficacy primarily evaluated at?

A. Well, there's been a shift over the last 25 years since the introduction of targeted drugs. This occurred in the mid '90s. And there's been a shift so that efficacy has been evaluated earlier and earlier in -- in the trials. And -- it was always evaluated. I mean, you always wanted to know whether patients were responding or not. And that was, as others have pointed out in the literature, it's a very important finding. But the possibility of actually approving drugs after Phase 1 never really occurred to people until the targeted drugs began entering the clinic in the mid '90s, and the first example was a drug that entered in 1999. And that was Gleevec, imatinib for CML -- and that was a milestone in oncology in the sense

that you could approve a drug with very, very early data. And that has become now a much more common thing so that the way we do trials has really radically altered in the last 20 years.

Q. In 1999, was it more true that effects on efficacy could only be evaluated in, at least, Phase 2 clinical settings?

A. I don't agree with that. You said the word "only." I would say usually the definitive evidence of activity occurred in Phase 2. But with Phase 1b trials, for example, you would always look at the efficacy in comparison to what you saw with the alternative schedules of Phase 1. And if it didn't look promising, you wouldn't continue. If you -- if you saw promising clinical activity in Phase 1b, you would often proceed with that trial.

Q. Now, you testified at a trial regarding the patent at issue in this IPR. Correct?

A. I'm afraid I don't understand your question.

Q. You gave testimony in front of a judge in Indiana a couple of years back --

A. I did.

Q. -- in a trial involving this case.

Right?

A. Yes.

Q. All right. And you were asked some questions at that trial --

A. Yes.

Q. -- right?

I'm going to show you Exhibit 1064 and ask you to turn to Page 7-1211.

(Excerpt of transcript of Dr. Chabner's trial testimony from August 26, 2013 marked Exhibit 1064.)

A. Mm-hmm.

Q. And feel free to review what you want, but I'm going to ask you to specifically look at Lines 6 through 9.

A. 1211. I don't see Line 69.

Q. Line 6 through 9.

A. Oh, okay.

Q. You let me know when you're there.

A. Yes.

Q. This is a transcript of your testimony --

A. Yes.

Q. -- at trial. Right?

And you were asked the following question:

"QUESTION: Now you agree that any effects on efficacy can only be evaluated in at least Phase 2 settings, right?

"ANSWER: I think that's a very broad statement. Now, I think it's certainly not true. In 1999, it was more true, yes."

Did you give that answer to that question?

A. That's exactly what I told you before. I said that we were in an evolution and Phase 1 results were becoming much more important in terms of -- and the reason was that we knew which patients to select.

But, yes, I would say that it's -- it was more true then, but it was not exclusively true. And that Phase 1 was a -- an important indicator of clinical activity.

Q. You're not disavowing that trial testimony. Correct?

A. No, I'm not.

(Article entitled "Trends in the Risks and Benefits to Patients With Cancer Participating in Phase 1 Clinical Trials" marked Exhibit 1065.)

BY MR. GABRIC:

Q. I'm going to show you what we've marked

as Exhibit 1065. And ask you if you recognize that document?

A. I do.

Q. You're ahead of me, Doctor. Thank you.

MR. GROSSMAN: So while the doctor is taking a look at this document, is this Exhibit 1064, is this some sort of mixture of two documents that have been compiled together?

MR. GABRIC: It's intended to be his Cross-Examination testimony. And that was the intent.

MR. GROSSMAN: Okay.

MR. GABRIC: Perhaps I can help you. I think what happened is his Cross-Examination started at the end of one day and then continued on to the next day. So maybe that's why it looks the way it does.

MR. GROSSMAN: Okay.

BY MR. GABRIC:

Q. You recognize that exhibit?

A. I do.

Q. What was the number again?

A. 1065.

Q. Thank you.

MR. GROSSMAN: And, Counsel, I'm going

to object to this document that it's not prior art. And unless you can cure that objection now, we're going to reserve the right to strike all testimony regarding it.

MR. GABRIC: Your objection is noted, Counsel.

BY MR. GABRIC:

Q. And what is this document, sir?

A. A paper.

Q. And you're an author of one of these papers?

A. I am.

Q. And what was the objective of this paper?

A. To look at trends in the rate of transfer-related -- treatment-related deaths, objective responses, serious toxicity and identify factors associated with these three outcomes.

Q. And why were you looking at that?

A. We just wanted to summarize recent experience in Phase 1 trials and what we could glean from it.

Q. And you looked at response rates in Phase 1 trials from a 1991 to 2002 time frame?

A. Right.

Q. All right. And these are Phase 1 trials of, what, cancer drugs?

A. Yes.

Q. And you found that there was a decrease in average response rates over that 12-year study, right?

A. I'd have to look at the chart. I believe that's correct, but I'd have to look at it.

Q. I'll point -- I'll try to help you out. On Page 2135, there's a Figure 2.

A. Right. I'm familiar with this.

Q. Right. And so what you found is from 1991 to 1994, there was a response rate of about, I don't know, 6 percent, 6.2 percent, I think. Right?

A. Yes.

Q. And then from the time 1995 to 1998, the response rate in Phase 1 trials went down. Right?

A. It did, but it was heavily influenced by the drug that was available in 1991, which was the drug we were developing, taxane, which was significantly active in Phase 1. So it

contributed unusual spike in response rates at that point. Which was very important. I mean, this was a clue that the drug was going to make it.

Q. And if you look at Page 2135, you see on the left-hand side it says "therapeutic response."

A. 2135. I don't know where you're talking about.

Q. Page -- it's the same page as Figure 2.

A. Oh, okay. Right.

Q. And you go to the left-hand side, under "therapeutic response."

A. Yeah.

Q. About seven lines down, what you wrote here is "at the trial level average response rates decreased significantly over the 12-year study period."

A. Mm-hmm.

Q. "Of 6.2 percent, parenthetical, end parenthetical" -- there's some language in there -- "in Period 1 to 2.6 percent in Period 2 and to 2.5 percent in Period 3." Right?

A. Mm-hmm. Yes.

Q. Then you graph that in Figure 2.

Right?

A. What?

Q. And then you graph that data in Figure 2.

A. Yes.

Q. All right. And then on the next page, in Table 4, you also note that the response rate to colorectal -- colorectal cancer went down over this 12-year time frame. Correct?

A. What was your conclusion?

Q. Do you see Table 4?

A. Yes.

Q. Do you see the first entry, colorectal? Colorectal?

A. Yes.

Q. Colorectal. I'm sorry, I mispronounced it.

A. Yes.

Q. And you evaluate the response rates in Phase 1 studies of cancer drugs for colorectal cancer. Correct?

A. Right.

Q. And the response rates went down over that 12-year period.

A. I see that.

Q. All right. And then in this paper, you tried to explain some of the reasons for the trend and the reduction in response rates. Correct?

A. I guess we did. I would have to look at it.

Q. All right. Go to Page 2138.

A. Mm-hmm.

Q. And the middle column, the last paragraph.

A. Can you give me a chance just to look through this?

Q. Yes. Take your time. I'm sorry.

A. Well, it discusses, first, the death rates, which were going down as the nature of the agents tested was changing in this time. And it's exactly the transition I was talking about that there were more targeted agents and the initial targeted agents actually were -- many of them were inactive. But -- the monoclonal antibodies -- let me review the rest of it.

Q. And you're free to review what you want. I'll kind of focus you on what I'm looking at to move this along as quickly as possible.

A. Okay.

Q. I'm at Page 2138, the middle column, the last paragraph. "We were surprised to see response rates decrease over 12-year study period -- over our 12-year study period. There are several potential explanations."

Do you see that?

A. Mm-hmm.

Q. And then you provide some of the potential explanations.

A. Yeah. Actually -- it actually addresses one of the major issues, this imatinib drug. We didn't look at the hematologic drugs. If we had looked at that one, the response rate was like 80 percent in the first trial. So, you know, it was a function of the drugs that were in the clinic at that time.

Q. So I want to focus on about, I don't know, one, two, three, four, five, six, seven, eight, nine, ten -- ten lines down where it says "second."

A. Mm-hmm.

Q. It says, "Second, because a number of standard treatments available to patients expanded over the study period, patients enrolling in trials during more recent years

tended to have had more prior treatment..." --

A. Mm-hmm.

Q. -- "...possibly contributing to drug resistance."

Do you see that?

A. I do.

Q. Okay. So what you're saying there is these patients in these Phase 1 trials that you were evaluating had been pretreated with other drugs and that could have affected their response rate?

MR. GROSSMAN: Objection to the form of the question.

A. It could affect it, but it entirely depends on the drugs you're testing. So if the drugs have something in common that would lead to common resistance, yes, it could affect it. But I don't think that's the explanation.

I always felt, when I wrote this paper, that it was heavily influenced by those two factors. One is the taxanes were in Phase 1 in the early '90s and they were very active drugs. And that was an unusually high response rate that we found in that one period, 6 percent.

Secondly, I think that the exclusion of

hematologic malignancies, which tend to be more responsive to cancer drugs, influenced the -- the data. So that if we had included, for example, imatinib, in the 1999 to 2002 period, the response rate would have been much higher.

So, you know, there are a lot of factors. I don't think this indicates the patients were becoming more resistant to treatment. That's possible for some of the drugs that were going into the clinic, but it was certainly not the case for -- now, we took many heavily pretreated drugs -- patients after this into Phase 1 trials and they responded beautifully if we had the right drug.

Certainly, you know, for specific agents, it could be a factor. Yes. But that's about, it's one of many factors.

Q. All right. So your testimony is there's many factors. I just want to make clear, though, that some of those factors include, number one, that these patients in these Phase 1 studies may have been subject to prior treatment with different drugs. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. That could be.

Q. That could be a factor --

A. Could be a factor. It wasn't -- all of this is speculative, you know. Rather -- there's no evidence. We didn't present evidence to support those possibilities.

Q. And another factor is, is that these patients who were pretreated with another drug prior to coming to these Phase 1 studies could have some drug resistance --

MR. GROSSMAN: Objection to the form of the question.

Q. -- correct?

A. That is possible. And it would make a difference if the drugs were of the same general class, yes.

And in the early days of chemotherapy where we were trying multiple alkylating agents it certainly would have been the case. As the '90s progressed we were bringing newer kinds of drugs into the clinic where that would be less of an issue.

Q. Now, you were asked about this paper at that trial we just talked about a little while ago. Right?

A. Yes.

Q. All right. And I'd like you to turn to Page 1206 of your trial testimony.

MR. GROSSMAN: Counsel, I'm going to object to 1064 to the extent I believe this exhibit was also addressed in Dr. Chabner's redirect, which is not part of this trial excerpt. So to the extent you sort of clipped bits of existing documents and compiled them into a new document, this Exhibit 1063 -- 1064 is both incomplete and not an accurate copy of the documents from which it's been excerpted.

BY MR. GABRIC:

Q. And just to give you con- --

MR. GABRIC: Your objection is noted, Counsel.

BY MR. GABRIC:

Q. To give you context, Doctor, if you turn to Page 1205 of your testimony --

A. Yes.

Q. -- around Line 9. Are you there?

A. I've got it.

Q. It says -- and if we turn to 2138, you've got the comment discussion. Right?

A. I don't see that. Wait a minute.

Q. Are you on --

A. What line is it?

Q. 1205, Lines 9 through 10.

A. Okay. Yes.

Q. All right. And so counsel is referring to Page 2138 of this paper you wrote, just to give you context. Okay?

A. Yes.

Q. And this is where you provide some of the reasons for the reduction in response rate in these Phase 1 trials you had observed in your study. Correct?

A. Mm-hmm.

MR. GROSSMAN: Objection to the form of the question.

Q. Then you were asked the following question, you gave the following answer. And I'll refer you to Page 1206 --

A. Mm-hmm.

Q. -- line 12:

"QUESTION: And so if the standard therapy changes, what you're saying here" -- this paper, this exhibit -- "the prior treatment that people had could change, and that could make it harder to see response rates later on because they had

better or different treatment ahead of the Phase 1 trial, right?

"ANSWER: Yes. It would also depend -- I think that's correct in terms of sequential chemotherapy because there is a cross resistance with drugs. The other factor is that the patient's tolerance to drugs may decrease with prior treatment. So, that certainly could be the case. However, it depends entirely on the kind of agent you're treating, so we found, for example, in lung cancer recently..." then you tried to go on and --

A. They cut me off.

Q. They cut you off.

But you gave that answer to that question. Correct?

A. At the trial --

MR. GROSSMAN: Objection.

A. -- yeah.

Q. You're not disavowing that testimony. Right?

A. That's exactly what I've been saying.

But -- but I would point out that this paper doesn't give the data to support that that was the major factor. That's one of a number of

potential factors.

MR. GROSSMAN: And, Counsel, again, since you failed to cure the objection, we reserve the right to strike all testimony about this document, 1063 or 1064 -- sorry, 1064 and 1065.

(Exhibit 2053 incorporated by reference.)

BY MR. GABRIC:

Q. Let me show you what we've marked as Exhibit -- you guys marked it, it's Lilly's Exhibit 2053.

And, for the record, this is the Von Hoff paper. Are you familiar with this document?

A. I am.

Q. You actually cite this document in your declaration.

A. Right.

Q. I'll give you a second if you need to-- are you ready?

A. Yes.

Q. Okay. Now, the Von Hoff paper, this is also a study of Phase 1 trials and response rates over a time period from, what, 1970 to 1983. Right?

A. Yes.

Q. And this paper was published as a result of an NCI contract?

A. I believe it was. I haven't looked at the -- who paid for it.

Q. Okay.

A. Oh, this was -- he was a Phase 1 contractor. So this study was not paid for specifically, no. He was a Phase 1 contractor.

Q. You oversaw the contract that led to this publication?

A. I did.

Q. All right. And on 2053, Von Hoff explained the materials he used in conducting his study. If you look under materials and methods.

A. Yes.

Q. He looked at published trials from complete studies. Right?

A. Mm-hmm.

Q. He did not use abstracts of Phase 1 studies.

A. Yes.

Q. So he excluded abstracts?

A. Yes.

Q. And what Von Hoff did here was if there

was multiple Phase 1 trials or schedules for a particular drug, he lumped them all together for purposes of his analysis. Right?

A. Yes.

Q. He did not compare a Phase 1 trial with a drug against another Phase 1 trial of a drug and draw any conclusions. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. I'm not sure I understand your question.

Q. Yeah. Let me -- let me ask a better question.

A. That's not clear.

Q. What Von Hoff did not do here, is he did not take a Phase 1 trial of Drug A, look at another Phase 1 trial of Drug A, compare them and draw conclusions about Drug A?

MR. GROSSMAN: Objection to the form of the question.

A. It's not in the paper. I don't know what he did himself personally. Probably he did but -- did that, but it's not in this paper.

Q. Well, in this paper what he did is he took those Phase 1 trials on Drug A and lumped

them together?

A. That's right.

Q. He didn't compare the two trials --

MR. GROSSMAN: Objection to the form of the question.

Q. -- right?

A. That wasn't the purpose of the paper.

Q. I understand.

I have that right. Correct?

A. Yes.

Q. And what Von Hoff concluded in this paper when he looked at all these Phase 1 trials is that there was about a 6.3 response rate, 6.3 percent response rate?

A. Right.

Q. I'm sorry. I didn't hear you.

A. Yes.

Q. Okay. And this included complete and partial responses?

A. That's right.

Q. And at Page 119, Von Hoff says in the sentence before the first full paragraph -- are you on Page 119 of his paper?

A. Yes.

Q. It says, "To date, there has not been

one compound which has made it to market which did not have at least one response rate in Phase 1 trials." Correct?

A. Yes, he does say that.

Q. So Von Hoff focuses on the fact of making sure that there was at least one response in a Phase 1 trial. That's the focus of his paper?

MR. GROSSMAN: Objection to the form.

A. I wouldn't say that's the focus of his paper. He just says that nobody made it to approval if they showed nothing.

Q. All right. Now you --

A. The opposite was also true. The more responses, the more likely it was going to work.

Q. Now, you were asked about this paper at that trial in Indiana, as well. Right?

A. Yes.

Q. And let's take a look at -- let's go to Page 1185. And I'm at -- starting at Line 3 --

A. Yes.

Q. -- you were asked the following questions about this paper and gave the following answers:

"QUESTION: Dr. Von Hoff concludes, 'To

date, there's not been one compound which has made it to market which did not have at least one response in Phase 1 trials.' Correct?

"ANSWER: That's true.

"QUESTION: And his focus is on making sure that there's at least one response there, correct?

"ANSWER: Right.

"QUESTION: And if we look at the data that's in Figure 2 on page 120, and we look at the 'marketed' column, correct?

"ANSWER: Right.

"QUESTION: It looks like there's at least two marketed that had one response in the entire Phase 1 set of trials, correct?

"ANSWER: It looks that -- it looks like that's true, yes.

"QUESTION: And it looks like there are six or seven marketed drugs with at least -- with less than five responses across all Phase 1 trials, right?

"ANSWER: Right. So what's your point?"

Did you give that testimony?

A. I did.

Q. And you're not disavowing this

testimony.

A. No.

MR. GROSSMAN: Counsel, again, I'm going to object. This article was addressed on Redirect. And to the extent you're trying to read testimony into the record, this exhibit is incomplete. You need to cure that objection. You haven't, so we reserve the right to move to strike.

Actually, Counsel, we've been going about an hour. Why don't we take a break.

MR. GABRIC: Sure. Yeah, I neglected to mention, any time you want to take a break, just --

THE WITNESS: Oh, really. Okay.

THE VIDEOGRAPHER: The time is 9:13. We're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: Here begins Disk 2 in the deposition of Bruce Chabner, M.D. The time is 9:26 and we're back on the record.

BY MR. GABRIC:

Q. Welcome back, Doctor.

A. Yes. Sorry.

Q. Something I neglected to tell you first

thing this morning, and I apologize. But under these proceedings, your -- during a break in your testimony, when we take breaks, you should not be discussing with your counsel the substance of your testimony.

Do you understand that?

A. I do.

Q. Okay. And I take it, did you follow that?

A. I did.

Q. Okay. I'm assuming your lawyers told you that before we got here today.

A. Yes. I've done this before.

Q. Okay. I just wanted to make sure. Fair enough.

Exhibit 1065, the Roberts paper, where you're a coauthor.

A. I don't know where it is. I'm sorry.

Q. That's okay. I hope we haven't lost it.

THE WITNESS: Is that it?

MR. GROSSMAN: This is it.

MR. GABRIC: Did you take that?

MR. GROSSMAN: I just gave it to him.

THE WITNESS: That's Von Hoff.

MR. GABRIC: I got them confused.

BY MR. GABRIC:

Q. That paper was published in late 2004?

A. Right.

Q. Okay. At that time frame, what, if any, relationship did you have with Lilly?

A. In -- I had very little to do with Lilly in terms of their clinical trials. I had a scientific relationship with Jerry Grindy, who was the head of their drug development for antimetabolites and particularly for the antifolates. I knew Jerry very well. He, unfortunately, died at an early age in the '90s. But I was familiar with their drug development program in the antifolates. But I didn't actually do clinical trials with their drugs, personally.

In about 1999 or year 2000, they began testing a drug called Forteo, which was a drug to improve bone strength and it was an analog parathyroid hormone. It was a fragment parathyroid hormone, and it since has been approved. And there was one problem with the drug and that was that in rats, with continuous treatment and relatively high doses, that the

rats developed osteogenic sarcomas. And I happen to know a good deal about osteogenic sarcomas in rat toxicology because of my experience at NCI. So they came to me and asked me what I thought of that, would that be a show stopper in putting the drugs into people. And I knew and colleagues at the Harvard dental school that I worked with knew that in rats, there was very active bone turnover throughout the -- much more active than in humans, throughout the life cycle. And that the possibility that stimulating that could lead to a tumor and that it would not necessarily extrapolate well to people. And that was sort of a general principle that when you see something in animals, you're not sure it's going to happen in people. It could happen in people. And they asked for advice about what to do. And I said, well, I thought it was a low probability. People are only going to take this for a year. Those people were -- the rats were taking it for their life cycle, the whole lifetime. So it's unlikely that this is going to be a problem. But what you ought to do is create a surveillance study.

So they went to the FDA and said we would like to market this but we propose to do a

post-marketing surveillance study. And this was, I guess, around 2001 to 2002. And so the FDA and Lilly both decided that I should be the chairman of a committee. I have known people at the FDA because of my position at the NCI for many years. There were three people who were, I mentored who became directors of the FDA. So they trusted that I knew what I was doing and they said, well, why don't you create a post-marketing study to evaluate this toxicity. And it was a novel study and it's still going on. And basically, I -- I chair a committee which meets twice a year. We review a lot of surveillance evidence of several different kinds. And these were studies that I helped design with the committee. They've shown no evidence of an excess of this tumor in patients treated. But the study is still going on and gives the FDA a regular report about this.

And it's something I do for Lilly, but it's also I'm doing it for the FDA. And I get paid for doing this, it's not a large amount of money, but it's a, you know, it's a regular committee job.

Q. So outside the context of the litigation over this patent, your relationship

with Lilly began around 1999?

A. This -- this -- yeah. Actually, it's a different division of Lilly. It's not with the cancer division. It's with the endocrine division.

Q. And so in the time frame from 1999 to 2004, you did have some financial relationship with Lilly?

A. Yes.

Q. As modest as it may be in your opinion?

A. Believe me, it wasn't enough to make my day.

Q. Okay. Understood.

Were you on, in the -- ever on any advisory boards for Lilly?

A. You know, I can't remember ever being on an advisory board. I was not on one of their major boards, no. I just can't remember if I -- you know, it's 47 years, you know, it's possible I might have done something with them.

Q. Let me try to refresh your recollection. If you look at Exhibit 1065, that's your paper we were talking about?

A. Yes.

Q. And there's a section at the end called

"Financial Disclosures."

A. Yes.

Q. What is the intent of a financial disclosure section in a paper?

A. Just to state where you've had -- make public where you've had some financial connection to a -- to a company.

Q. And why is that done?

A. Just to advise the readers that this, you know, this existed. Yes.

Q. And why do the readers, why do they need to be advised about that?

A. It's a potential conflict of interest.

Q. And here you say -- well, the paper says "Dr. Chabner has consulted for or served on the advisory boards," and it lists quite a few companies.

A. Yes.

Q. And one of them is Eli Lilly. Does that refresh your recollection?

A. That's the Forteo. Yes.

Q. Okay. So that was an advisory board that you were on?

A. No, it's not an advisory board. It was a committee set up by the FDA and Lilly for

post-marketing surveillance, but I was paid.

Q. Okay. What I'm trying to understand, Doctor, is it says here "Dr. Chabner has consulted for or served on."

So Lilly is the consulted part of this?

A. That's right.

Q. Thank you.

A. It's not an advisory board in the sense that I was telling them how to develop a drug.

Q. Aside from this lawsuit and is the drug you mentioned, any other relationship with Lilly over the years?

A. I have friends that work there.

Q. You, personally?

A. I grew up very close to Indianapolis. Always appreciated the presence of Lilly as an employer in our area.

Q. You like Lilly, I take it?

A. Yes. You know, I have no special like for Lilly. I like companies that actually do something useful for cancer patients. Not all of them do. And Lilly has.

(Exhibit 1014 incorporated by reference.)

(Exhibit 1015 incorporated by

reference.)

BY MR. GABRIC:

Q. I'm going to show you or hand you the Hammond extracts. I suspect you're familiar with those.

A. Yes.

Q. And for the record, those are Exhibits 1014 and 1015. And I think colloquially we've referred to these Hammond abstracts as Hammond I and Hammond II.

Are you familiar with that nomenclature?

A. I sometimes get it confused, I must admit.

Q. Yeah, well --

A. I can't always remember what the difference is between Hammond I and Hammond II.

Q. Join the confused club. I do, too.

Exhibit 1014. That's what I believe we've been calling Hammond II.

A. Right.

Q. And Exhibit 1015 is what we have been calling Hammond I, I believe. Is that correct?

MR. GABRIC: If I have that wrong, Counsel, please let me know.

MR. PERLMAN: I'm certain that the one

that you would intuitively think is "I" is going to be II and vice versa.

MR. GABRIC: Right.

MR. PERLMAN: We've just been going with the exhibit numbers just to kind of keep it straight.

MR. GABRIC: All right. Okay. Thank you, Counsel.

BY MR. GABRIC:

Q. Let me ask you a question, Doctor. Exhibit 1015 reports on some clinical one -- Phase 1 clinical results for, I believe, 33 patients. Right?

A. Yes.

Q. And Exhibit 1014 reports some results, Phase 1 results for 21 patients. Right?

A. Right.

Q. Now, is it your understanding that Exhibit 1015, those 33 patients, those include the 21 patients that are referred to on Exhibit 1014?

A. Yes. I think it's the same study.

Q. And so the Hammond -- I'm sorry, the Hammond, Exhibit 1014, reports a partial response in connection with therapy with pemetrexed and

pretreatment with folic acid. Correct?

A. Right.

Q. And that one partial response in Hammond abstract is over the Von Hoff line of zero or one or more. Correct?

A. It's one.

Q. So it meets the Von Hoff threshold?

A. I have never heard it called the Von Hoff threshold.

Q. Okay. It's over the -- it's over the Von Hoff line.

MR. GROSSMAN: Objection.

A. I would say it's one response.

Q. Now, you -- you were asked about the Hammond abstracts at the trial in Indiana. Right?

A. Yes.

Q. Turn to Page 1209. Let me know when you're on Page 1209.

A. I'm there.

Q. All right. Refer you to Line 11.

A. Okay.

Q. I'm going to read from line 11 to 14. And you were asked the following question:

"QUESTION: So you agree that the one

partial response in the Hammond abstract is over the Von Hoff line of zero or one or more?

"ANSWER: Well, I agree, and we looked at the chart and seen what one implies," then you said, "which is low probability of success."

Right?

A. Yes.

Q. So you testified it was over the Von Hoff line, one partial response.

A. You know, as I said, there is no such thing as a formal Von Hoff line. There is one response. And I -- I agree that there's one response.

Q. And you're not disavowing that trial testimony?

A. No, not at all. I said there's a low probability of success for one response.

Q. Now, have you ever published the results of a Phase 1 study where you did not report any responses, yet the drug warranted further study?

A. I -- I couldn't answer that question. I don't have -- my memory isn't -- I can certainly remember studies where we did Phase 1s, actually a Phase 1b, where there was no responses

and the drug died.

Q. And do you recall ever publishing where you did not report any efficacy but nonetheless, in the published document, you suggested that further work be done?

A. Well, that's entirely possible. It depends on the circumstance and, you know, the drug and the alternative schedules and -- yes.

Q. So one of skill in the art in 1999 would understand that just because you had no reported efficacy at a Phase 1 clinical trial would not necessarily mean that you should shelf the drug?

A. As I said, I agree with that. Because it entirely depends on what drug you're testing, what you know about the drug, what you've done before with the drug. Are there -- are there alternatives that you might want to explore with that drug? Each drug is a major investment. And part of the sponsor. And you know, the decision on which way to go with the drug is a very complex decision, but it depends on a number of factors.

Q. And, in fact, Von Hoff even reported that if you got one response in a Phase 1

clinical trial, you still may make it to market?

A. Well, as I said, and you questioned me, responses are important in Phase 1.

Q. And Hammond got a response?

A. One response.

(Article entitled "Phase 1 and Pharmacokinetic Study of the Multidrug Resistance Modulator Dexverapamil With EPOCH Chemotherapy" marked Exhibit 1066.)

BY MR. GABRIC:

Q. I'm going to show you what we've marked as Exhibit 1066. Do you recognize this document?

And, for the record, you're a coauthor?

A. Oh, yes. I know this study very well.

Q. All right. And you're a coauthor on this study.

A. I am.

Q. And this was published in 1995?

A. Yes.

Q. And did you report any efficacy results in this study?

A. No. But the reason was that virtually all the patients responded.

Q. You don't --

A. It's a well-established regimen, EPOCH.

Q. You didn't report that in the paper?

A. No. Because it's an accepted regimen. It's -- you know, we use it all the time. It was actually asking a pharmacokinetic question. Could we achieve dose levels of verapamil that would potentially modify multi-drug resistance. And it answered a number of pharmacokinetic questions. It was not designed to look at response endpoints, because there were -- we knew there were lots of responses to EPOCH. It's a standard regimen.

Q. So this was a clinical Phase 1 trial?

A. It was a Phase 1 in dexverapamil with this established regimen, which is not a Phase 1 regimen. It -- part of it is Phase 1. Yes.

Q. It wasn't designed to evaluate efficacy. Correct?

A. It was a pharmacokinetic study. Yes.

Q. Which is different than evaluating efficacy?

A. Yes.

Q. And you didn't report any efficacy results in this paper. Right?

A. No. As I explained, this is a well-established regimen. It was known to be

efficacious.

Q. I understand you have reasons that you're giving why you didn't do that. But I just want to be clear, it's not reported in the paper, the efficacy. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Yeah.

Q. All right.

A. I should also inform you that dexverapamil is not an anticancer drug. Do you und- -- I mean, that's important to understand in this. We're not evaluating a drug which is -- is a -- an anticancer drug.

Q. And if you look at the -- the conclusion, without reporting any results on efficacy, you report here -- how do you pronounce that dex -- how do you pronounce it?

A. Dexverapamil.

Q. Okay. We'll go with your pronunciation. Should be considered for further study. Right?

A. Yes.

Q. So I just want to make sure I understand the paper. There's no efficacy

results published in this paper. Yet this paper says it should be considered for further study. Right?

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. I have that right?

A. Yes, you're right.

Q. Now, I want to go back to the Hammond abstracts. Now, I'm one of ordinary skill in June of 1999, okay? And I'm reviewing these Hammond abstracts, Exhibits 1014 and 1015.

You got the context?

A. Got it.

Q. All right. Now, the Hammond abstracts don't report to one of ordinary skill in the art the dosage that was received by the patient -- the dosage of pemetrexed that was received by the patient who manifested a partial response. Correct?

A. It doesn't. It doesn't identify that patient.

Q. It doesn't identify the dosage of pemetrexed that that patient received. Correct?

A. That's right.

Q. All right. And the Hammond abstracts do not report the number of courses that each patient received in this study. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. I'd have to read it carefully to find out. Yeah. I -- I thought it did say something about that. 21 patients received 55 courses.

Q. Well, each patient didn't receive 55 course, right?

A. No, 21 patients received 55 courses. So it's an average of about 2.8, 2.9.

Q. But we don't know what each patient received?

A. No, we don't. No. Absolutely, we don't. I mean, that would be impossible to report in an abstract.

Q. Because abstracts are limited to a certain number of words. Right?

A. Yes.

Q. And I believe Exhibit 1015 reports that there was 90 courses spread over 33 patients. Right?

A. The same. 2.8 percent. 2.8 cycles per patient, yeah.

Q. But we don't know -- I mean, nobody got 2.8 cycles. Right?

A. Well, no. Some got three. Some got two. Some got four. Yeah. Right.

Q. Now, were there any controls put in place in the Hammond abstracts that would permit one of ordinary skill in the art to make a quantitative comparison of the results in this Phase 1 trial on pemetrexed to a different or another Phase 1 trial on pemetrexed?

A. Well, there is no formal control in a Phase 1 study, however, one does look at the results and compare it with what one knows about the drug in prior trials and tries to draw conclusions about how valuable this new regimen would be as compared to the others. That's a -- that's a standard business decision. It's a scientific decision. A lot of things enter into that decision.

Q. And I understand your opinion, Doctor. But I just want to make sure that I'm not misunderstanding Hammond. Okay.

So one of skill in the art in 1999, as of June of 1999, they would understand that the Hammond trials were not statistically designed to

permit quantitative comparisons of the results in the Hammond trials to another Phase 1 trial --

A. No.

Q. -- on pemetrexed?

A. No. That's true. One response is statistically no different than zero responses.

Q. But the studies weren't statistically -- or set up to permit a quantitative comparison to other Phase 1 trials. Correct?

MR. GROSSMAN: Objection.

A. That's correct.

Q. There were no controls put in place either to permit a quantitative comparison of the results in these Phase 1 trials depicted in Hammond versus other Phase 1 trials of pemetrexed?

MR. GROSSMAN: Objection.

A. Well, I don't totally agree with that. I mean, there are some controls in the sense that the investigators have done other trials with the drug. They've -- they're selecting from a patient population that's quite similar, not -- probably not identical, but it's hard to make it identical. It's not a randomized study. And

they have, you know, prior knowledge of what the drug has done in other trials. So while a comparison is not statistically significant and -- and absolutely quantitative, the results are important, both in terms of toxicity and the response rate.

Q. Well, you mentioned patient populations. We don't know the details of the age, the condition of these patients, their prior treatments. There could be substantial differences between the patient populations in the Hammond study versus other Phase 1 studies of pemetrexed. Isn't that true, sir?

A. I -- I doubt if there will be substantial differences. They're all patients with advanced solid tumors and primarily lung, GI, maybe some breast cancer. But lung and GI are the predominant ones. There's a smattering of other tumors. That's true.

Q. Now, you were asked about the Hammond abstracts at that trial in Indiana. Correct?

A. I guess I was. Yes.

Q. And -- strike that.

So let me ask you this question: Phase 1 trials, in general, you said there are no

controls put in place. Correct?

MR. GROSSMAN: Objection.

A. I think that's a very global statement. Of course, there are controls. The whole thing is reviewed by the FDA before you do it. It's done under regulation.

Q. I'm sorry. I --

A. What -- what do you mean?

Q. That was a poor question.

A. Do you mean a randomized control?

Q. There's no controls put in place to permit comparing one Phase 1 clinical trial to another Phase 1 clinical trial?

MR. GROSSMAN: Objection to the form of the question.

A. I think that the word "control" in the clinical trials space implies that there's a comparison to be made. It isn't -- it isn't only a randomized study that's controlled, there are historical controls which we use all the time. They're less exact, but they're part of the controls that we use in judging the outcome of a study.

Q. Right. And all I'm getting at, Doctor, is these Hammond abstracts, the clinical Phase 1

trial here, this was not designed for the purpose of making comparisons between the results in this trial to the results in a different trial of pemetrexed. That was not your objective?

MR. GROSSMAN: Objection to the form of the question.

A. I don't agree with that at all. You don't ignore what you know about the drug. And when you do the trial-- this is not the first Phase 1. So when you do the trial, you have a background of information about the drug. And you certainly would look at this in comparison. I mean, the toxicity obviously is going to be compared to what you've done before. I think you agree with that. And the clinical outcome, the response rates are also important to compare.

Q. I understand your opinion, Doctor, that it's your opinion, one skilled in the art would compare Phase 1 trials. I understand that.

All I'm trying to understand is: Do you agree that one skilled in the art would understand that these studies in Hammond were not structured and designed, from a statistical perspective, to make quantitative comparisons of the results in these -- in this trial versus a

different Phase 1 trial in pemetrexed? It wasn't designed for that purpose?

MR. GROSSMAN: Objection to the form of the question.

A. So there -- there is no built-in randomization that would allow you to make a p-value out of this, absolutely. A statistical comparison. However, you do have a body of knowledge and when you do a Phase 1 study, you are -- obviously will compare it. It isn't an absolute statistical comparison, because you don't have a simultaneous randomized control group for an alternative regimen.

Q. And as of June of 1999, are you aware of any study that was set up with the appropriate controls in place to make a quantitive comparison of the efficacy of pemetrexed, both with and without folic acid supplementation?

MR. GROSSMAN: Objection to the form of the question.

A. Well, I'm not -- I certainly can't say -- I don't know of such a trial. I can't say that it didn't exist, but I don't know of such a trial. And I doubt if it would ever be done that way, prior to 1999. I think probably post-'99,

there are examples of that, yes. But I'm not personally aware of one.

Q. Now, Hammond does not report whether the patient with the partial response was heavily or lightly pretreated with folic acid. Correct?

A. True.

Q. And it does not report whether the patient with one partial response was heavily or lightly pretreated with a prior chemotherapy treatment. Correct?

A. I haven't looked carefully at this, but -- I think it's a typical Phase 1 population, which it would be a pretreated population. It sort of depends on the disease because in some diseases, there is no standard therapy, they would go into a Phase 1 trial, particularly at this time. It's almost 20 years ago.

Q. Right.

A. Other patients would have therapeutic options prior to entering this kind of a trial. And I think this was a colon cancer patient, so it's likely this patient got a 5-FU regimen.

Q. But we don't know.

A. We don't know --

Q. We're guessing.

A. -- it's not stated.

Q. Hammond doesn't report to one skilled in the art in 1999?

A. No, we don't know.

Q. This patient with a partial response, we have no idea what prior chemotherapy pretreatment, if any, this patient had received?

A. You're right.

Q. You don't know much about this patient, based on the report?

A. I don't know --

MR. GROSSMAN: Objection to the form of the question.

A. I don't know much about this patient. That's for sure.

Q. One skilled in the art in 1999 wouldn't?

A. Right.

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. All we know is they received a partial response.

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. So I --

MR. PERLMAN: Is there a question? I can't tell.

Q. I don't know -- I don't know if the doctor is looking to answer something.

A. No. I'm waiting for you to ask a question.

Q. Okay. I didn't want to interrupt your thought process. I thought you were looking for something. I apologize.

Now, in Paragraph 98 of your declaration, you -- you're free to go there, but my question is pretty straightforward. You refer to the Hammond study as a Phase 1b study.

A. Mm-hmm.

Q. Why do you refer to Hammond as a Phase 1b study?

A. Because it's a study conducted after the initial group of Phase 1s. And there are a number of those, exploring different regimens. And this is another -- it's another option or alteration of the original schedule. So it's a derivative study. It's the same dose. It's a weekly -- or an every-three-week schedule. It's

an attempt to dose escalate in the presence of folic acid. But it's essentially a derivative study of earlier trials. So you don't have to start off with, you know, 50 milligrams per meter squared or 75, 100, 150. The whole thing that you would do on an initial Phase 1 trial.

And this has become a very common way of doing clinical trials. 1b gets through the IRB much quicker than a Phase 1. It usually knows where it's going in terms of the objective. It's a -- it's a study which can be finished relatively quickly compared to many Phase 1 studies.

Q. So we're probably all sick of hearing 1 versus 1b. I'm just trying to get an understanding though.

You look at Exhibit 1014 and 1015 and the title says a Phase 1. It doesn't say a Phase 1b.

A. No.

Q. Do you have any explanation for that?

A. Yes. My view of this is a Phase 1b and I think most of my colleagues would regard it as a Phase 1b.

Q. What would one of ordinary skill in the art consider this to be?

A. A Phase 1b.

Q. A Phase 1b.

A. Well, if a person had my experience, and I assume that a POSA would, they would think of it as a Phase 1b, because it's -- yeah. Phase 1 is a very broad label. There are different kinds of Phase 1s. And this is what I'm saying is a Phase 1b.

Q. So Phase 1b in your view is a subset of Phase 1s?

A. Yes.

Q. Now, would you agree that a person of ordinary skill in the art, as of June of 1999, would expect that pretreating with folic acid would decrease the toxicity of an antifolate?

A. Yes. In my opinion, it would decrease the toxicity, both for the tumor and the patient. For the host tissues.

Q. Right. So I just want to make sure. We may have some common ground in this case. And I'm trying to explore it.

A. That would be wonderful.

Q. Yeah, wouldn't it?

A. Okay.

Q. And I think this is an area of common

ground, but I want to make sure.

A. Yeah.

Q. So we're on the same page, one of ordinary skill in the art in June of 1999 would have an expectation that pretreating with folic acid would reduce the toxicity of an antifolate?

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. Right?

A. That's right.

Q. And I think there's some more common ground here. Let me explore it.

Would you agree that a person of ordinary skill in the art, as of June of 1999, would have expected that pretreating with vitamin B12 would decrease the toxicity of an antifolate?

A. I think that there is much less experimental data for that, but there was data that it could reverse the antitumor activity of antifolates. Yes. So that that's a reduction in toxicity.

As far as the effect on people, I don't -- I wouldn't know. I would think that it possibly would, because it -- it elevates reduced folate

pools when you give B12, you expand the pool of reduced folates. So it should have the same effect on normal tissue, but we're not -- I don't know as much experimental evidence for that as I do for the reversal of the antitumor activity.

Q. Okay. So let me just make sure.

So as of June of 1999, the person of ordinary skill in the art would have an expectation that pretreating with folic acid would reduce the toxicity of an antifolate on normal cells?

A. Right. Of an antifolate. Yes.

Q. And the answer may be yes, it may be no, but my question now is directed to Vitamin B12.

Would a person of ordinary skill in the art, as of June of 1999, have a reasonable expectation that pretreatment with Vitamin B12 would reduce the toxicity of an antifolate on normal cells?

A. Yes, it could. It would depend on the circumstances, though. I would -- can I qualify my answer?

Q. You're the witness.

A. Okay.

Q. All right.

A. So the witness would say that it would depend on the status of the folates in -- I think it would -- if a person were B12 deficient, it certainly would. If a person were B12 replete, it might not -- might have very little effect. And the reason I say that is the folate pools, the reduced folate pools would then be, in that person, may be fully adequate to -- to deal with the drug in the normal cells. But we wouldn't know. You'd have to try it. I think it has the potential of reducing toxicity in the patient that has B12 deficiency. But, as I said, it also has the potential of reversing the antitumor activity.

Q. Understood.

Okay. Moving right along here.

(Exhibit 2031 incorporated by reference.)

BY MR. GABRIC:

Q. I'm going to show you what we -- what Lilly marked Exhibit 2031. You talk about this document in your declaration a little bit. It's Laohavinij. I don't know how everybody else pronounces it. Somebody has a better idea.

MR. PERLMAN: Do you want to know?

MR. GABRIC: Yes.

MR. PERLMAN: We have been calling it "Laohavinij." The correct pronunciation is Laohavinij, or something of that sort. But we made a gentlemen's agreement to call it Laohavinij as long as Dr. Calvert is not around, because he's the only one who knows him.

MR. GABRIC: Okay. We're good with that. Thank you, Counsel.

THE WITNESS: I get the L and the H mixed up and I call it "Halloween."

BY MR. GABRIC:

Q. Now, this is a -- this is a paper that you cite in your declaration. Right?

A. Yes.

Q. I think it's a Paragraph 100. Let me turn there real quick. I think you cite this paper to support your, and correct me if I'm wrong, your comparison of the Hammond abstracts to the -- I believe the Rinaldi Phase 1 studies.

A. To the what studies?

Q. The Rinaldi?

A. Oh, that's a little bit complicated, that question. I'm not sure what you mean.

Q. Let me ask it this way.

A. Okay.

Q. You point to Laohavinij as providing support for the notion that one of ordinary skill in the art would compare Phase 1 clinical trials and draw conclusions about efficacy.

Have I got that about right?

A. I think it's a little more specific than that. It would be useful in a decision whether to proceed forward with the new schedule.

Q. What do you mean by that?

A. Well, should -- should we make an attempt to further explore the new -- new schedule of administration with folate supplementation versus the old schedule, which was 500 milligrams per meter squared, without folate, for pemetrexed.

In this case, for lometrexol, they tried folate supplementation with their GARFT transformylase inhibitor and got a very negative result. And I think they had one response and decided not to go forward with that schedule as a -- as a treatment option.

Q. Okay. So you point to Laohavinij and what Laohavinij reports is clinical Phase 1 with lometrexol?

A. That's right.

Q. Both supplemented and unsupplemented with folic acid?

A. Well, I have previous experiment with unsupplemented lometrexol. Now they're trying it with the folic acid supplementation.

Q. Okay. And you cite to Page 333 of Laohavinij. And it's 100, Paragraph 100 of your declaration, if you kind of want to get your bearings.

A. Yes.

Q. And you quote -- you quote from Page -33, the right-hand column, second full paragraph.

A. Yes.

Q. Going about halfway down it says, "clinical responses." Do you see that?

A. Yes.

Q. All right. And in your declaration, you quote the following portion: "Clinical Responses, which were observed in early Phase 1 studies of lometrexol given alone, have not been common in the current study; i.e., only one objective partial response has been observed...."

You kind of left out the rest of the

sentence.

A. Right.

Q. All right. Now, does he report in here what the number of responses were in the Phase 1 studies of lometrexol given alone?

A. I don't think he does. I don't know. I'd have to read the paper to say whether he did or not.

Q. Would one of skill in the art draw the following inference that, when he says it's not even common -- okay, that means it was more or less than one. Just wasn't one.

MR. GROSSMAN: Objection to the form of the question.

A. It says one. It really does say one.

Q. He says one in the folic acid supplement.

A. Right.

Q. He just says the unsupplemented was not common.

MR. GROSSMAN: Objection to the form of the question.

A. Where do you see that?

Q. He says, "Clinical Responses which were observed."

A. It was not common in the current study, one. And it contrasts that with the fact that partial responses were seen in the other studies.

Q. How many?

A. A number of them. I'd have to get the papers out. But I think it was 3, 4, 5, maybe even 10. I don't know.

Q. Does he report to one of skill in the art in June of 1999 --

A. Well, those studies are in the literature. You know, we could get those out and look at them.

Q. Well, you didn't put them in your declaration and talk about them --

A. But I know --

Q. -- about the responses.

A. But I know that they were there.

Q. Now, he -- the part you left out of your declaration is Laohavinij tries -- goes on to explain why maybe you didn't see the same response rate with folic acid. Doesn't he?

He goes on to say, "However, as the MTD" -- maximum tolerated dose, right? -- "has not been achieved, it could be argued that optimal therapeutic conditions have not been defined."

Right? That's what he says.

A. Let me put it this way: My answer to that is that a person of ordinary skill would know once you've escalated 30-fold in the dose, you can go on forever and you may never reach. And I think that you just can't take patients, they're not mice, you can't put 100 patients on to begin to see one response or two responses. At some point you make the decision to just say, it's not working. And I think that's what they did. They felt that they couldn't achieve a dose which would give them therapeutic usefulness.

Q. Well, he doesn't report in this paper that you shouldn't continue to pursue pretreatment with folic acid. Does he?

A. But that's what they did.

Q. Are you aware that there were subsequent studies with lometrexol with folic acid pretreatment?

A. I'm not aware of that. But it didn't work.

Q. Okay. So you -- is that reported in the literature, prior to June of 1999?

A. You know, I'm not sure.

Q. Okay. So I want to talk about one of

ordinary skill in the art in June of 1999, not about what you knew personally. All right? Can you do that for me?

A. Well, yeah. I'm trying to get the relevance here.

Q. Yeah. Well, maybe the relevance will become clear in a second.

So as of June of 1999, I'm one skilled in the art, I pick up this paper and what Laohavinij is telling me is that the reason why I may not have gotten as many responses with folic acid pretreatment is I haven't tested the maximum tolerated dose yet. And I may improve my results if I do that. Do I have that wrong?

MR. GROSSMAN: Objection to the form of the question.

A. It's potentially possible, yes.

Q. And nowhere in his paper does he say, Do not pursue folic acid pretreatment of lometrexol. Does he say that to one skilled in the art in this paper?

A. No. But I think they have to make a decision as a company where they're going with the drug. And it's -- you can't -- I think -- I hope I explained to you adequately that you can't

just keep expanding a trial with no responses. Because these are cancer patients. These are your relatives that are going on these patients. Do you want your own family to be exposed to a regimen which has failed in 32 of 33 patients?

Q. Does he report the number of patients that the -- well, he doesn't say the folic acid pretreatment failed. He doesn't say that in his paper, does he?

A. What he says is it reverses the toxicity of the normal tissue. Yes.

Q. Where does he say that? Where's it at?

A. I think he says, that's a -- that's a good thing. That's what they were looking for. But he doesn't see any clinical responses, because it's ablating the cancer, anticancer activity.

Q. It's your opinion, sir, that Laohavinij is telling one of ordinary skill in the art that folic acid obliterated the cancer activity of lometrexol?

A. He hasn't seen any. He reports that. He saw one response in 33 patients.

Q. And he provides a possible explanation for why he hasn't seen it. Correct?

A. That's right.

Q. And he says, "We may not have achieved our maximum tolerated dose." That could be the reason why. Right?

A. Yes. And my understanding is it would take another 33 patients to try to get there and you probably wouldn't see anything. So they -- they just made a judgment. You know, you have to make judgments in doing clinical trials.

Q. Other --

A. I think a person of ordinary skill would say, this is not a productive line of -- of research.

Q. Other than this statement about maximum tolerated dose, does Laohavinij provide any other reason why he didn't see --

A. Again, the reason is obvious. The drug is reversing -- the folic acid is reversing the drug's toxicity. And you said that to me and I said I agree with you.

Q. And the reason he reports, though, is that -- let me ask it this way:

Does he suggest that maybe you should explore the maximum tolerated doses in this pretreatment therapy and see what we get?

A. It's possible to do that, but his -- his superiors didn't agree with that, obviously, they didn't do it.

Q. Well, we don't know what his superiors did or didn't do. All we know is what he said in this paper. Correct, Doctor?

A. I guess you're right. The only thing I know is the drug -- the drug was dropped.

Q. Well, do you know why the drug was dropped?

A. Yeah, because it was not active.

Q. Well, are you sure about that?

A. I'm pretty sure about that.

Q. Didn't they find something that was more active?

A. Pardon?

Q. Didn't they find something that was more active than lometrexol?

A. There still is no drug for GARFT transformylase. They -- they tried a different compound, yeah.

Q. Yeah, but that different compound was more active --

A. It didn't work.

Q. But it was more active than lometrexol

and that's why they dropped lometrexol. Isn't that true, Doctor?

MR. GROSSMAN: Objection to the form of the question.

A. I don't know. This is -- this is a side conversation between you and me. All I know is neither one of the drugs proved to be useful.

(Sandoz Exhibit 1012 incorporated by reference.)

BY MR. GABRIC:

Q. I'm going to show you what's been marked as Exhibit 1012 in these proceedings.

And, for the record, this is a chapter from a book by Jackman. It's Chapter 12, Mendelsohn. And this was published, I believe June of 1999 is my understanding. It's got a copyright 1999. But my understanding it's June. If I'm wrong, somebody can correct the record at some point. Before June of 1999. And I ask you to page -- turn to Page 277.

(Witness complies.)

Q. And about four lines down, it says, "In preclinical models of efficacy, LY309887 appears to be more active than lometrexol in two pancreatic xenografts in the LX1 lung model.

Therefore, on completion of the preclinical toxicology for the compound, Eli Lilly decided to discontinue development of lometrexol in favor of developing LY309887."

Do you see that?

A. I do see that.

Q. So this is the reason why Lilly dropped lometrexol. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. No. The reason Lilly dropped lometrexol is it wasn't working.

Q. But this is what is reported in the literature as of June of 1999.

A. You wouldn't have dropped it if it were a good drug.

Q. As of June of 1999, one of ordinary skill in the art, with the prior art available to them, would understand that Lilly dropped lometrexol because LY309887 was more active. Isn't that correct?

MR. GROSSMAN: Objection. Asked and answered.

A. I don't know if it was more active. It was -- it was a tighter binding inhibitor. But

it was to be found out in the future whether it was useful or not. And it turned out that neither one of the drugs were useful.

Q. Well, it says right here, that LY309887 appears to be more active than lometrexol.

A. Active in what sense?

Q. It tells you. Two pancreatic xenografts in LX --

A. That's preclinical information, and it doesn't tell you that it's going to work in people.

Q. Well, this is what one of ordinary skill in the art had available to them as of June of 1999 --

A. Yeah.

Q. -- why lometrexol was dropped. Isn't that correct?

MR. GROSSMAN: Objection to the form of the question.

A. I don't -- I don't -- I think that's not the story. The story with lometrexol is it didn't work and they had to find a better drug and they went to L, whatever, 887. That's -- that's a very logical decision to try something that is a tighter binding inhibitor. But I think

you're avoiding the obvious conclusion that lometrexol didn't work.

Q. Are you aware of anything else that was published in the prior art prior to June of 1999, aside from the exhibit I just showed you, that reports as to why lometrexol was dropped?

MR. GROSSMAN: Objection to the form of the question.

A. No, I'm not.

Q. All right. Now, let's -- I'm going to show you another document that you referred to in your declaration.

If you guys have a better pronunciation, I'm all ears. Vidal, Vidal. It's Exhibit 2016.

A. Yes. Yes.

MR. GROSSMAN: I think you mean 2032?

MR. GABRIC: Oh, I'm sorry. Yeah. 2032. Thank you, Counsel. Too many numbers floating around here.

(Lilly Exhibit 2032 incorporated by reference.)

BY MR. GABRIC:

Q. All right. You refer to this document in, I think, Paragraph 89 of your declaration, and maybe elsewhere, okay?

What is Vidal? Where is it from?

A. It's a compendium in France that is used by doctors in -- in making decisions about what drugs to use and how -- how to dose them.

Q. Have you ever cited Vidal in any of your publications?

A. No. I, unfortunately, don't read French.

Q. Now, have you -- are you aware there's something called the Physicians Desk Reference, PDR, in the United States?

A. Yes.

Q. Is that kind of the what would be the counterpart to Vidal? The U.S. counterpart?

A. Yes. It's -- it's used in a similar way. Yes.

Q. All right. Did you look at the PDR to see if you could find any statement in the PDR similar to the statement in Vidal that you rely on?

A. No. Although I'm aware that other PDR-type compendia have this similar statement in Europe.

Q. Did -- have you reviewed the Physicians Desk Reference, though? Did you go looking for

that?

A. I think I did. Yes.

Q. And you didn't find it, did you?

A. No, I didn't.

Q. Now, Vidal, the statement you rely on, it says, "malignant tumor" -- and let me back up.

This is -- this is entry for cyanocobalamin -- cobalamin is that the pronunciation?

A. Cyanocobalamin. Yeah.

Q. I'm going to have a hard time today with some of these words. I apologize.

Now, there's a contraindication, it says, "Malignant tumor. Due to the action of Vitamin B12 on the growth of tissues with a high rate of cell multiplication, the risk of exasperation must be taken into account." Right?

MR. GROSSMAN: Sorry, Counsel. What page are you talking about?

MR. GABRIC: I'm sorry. Page 29.

BY MR. GABRIC:

Q. And you rely on that statement?

A. I think it's an accurate statement.

Q. I'm sorry.

A. I think it's an accurate statement.

Yes.

Q. Right. And you went looking for a similar statement in the PDR. Right?

A. Right.

Q. You didn't find it?

A. That's right.

Q. And there's multiple entries for products with Vitamin B12. Aren't there?

A. Yes.

Q. And none of them have the statement or anything similar to it, do they?

A. Yes. But I rely on this statement.

Q. How did this statement come to your attention?

A. It was pointed out to me through the -- preparation through the trial, but I'm aware of a number of studies that support this.

Q. So the lawyers found this statement?

A. No. I know the people. I know the people that did the experiments that show this.

Q. And I'm asking you about the statement, though, in Exhibit 2032. When was this statement first brought to your attention?

A. During the preparation for the -- the trial.

Q. Okay. During the preparation with the lawyers?

A. Yes.

Q. So the lawyers brought that statement to your attention?

A. Yes. They did a very careful search and they found it.

Q. And then you went out and tried to find a similar statement in the PDR?

A. I think it was brought to my attention by the people that were on the Teva side.

Q. What was brought to your attention?

A. That a PDR didn't contain the statement.

Q. Now, the statement in the Vidal reference, there's no citation to any authority or studies for that statement. Correct?

A. Yes.

Q. Is that correct?

A. It doesn't contain citations. But I'm personally aware of -- of the relevant experiments. I could tell you about them, if you want to know.

Q. So one in June of 1999 reading this statement is not directed to any studies or

publications in Vidal for support?

A. No, but I think it would prompt a person to look for those studies, and they were there. As I said, I can give you the names of the authors.

Q. That's --

A. You don't want that?

Q. I -- I don't.

A. Okay.

MR. PERLMAN: When you find a convenient time.

MR. GABRIC: This is convenient. This is fine.

Take a short break.

THE VIDEOGRAPHER: The time is 10:27. We're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: Here begins Disk 3 in the deposition of Bruce A. Chabner, M.D. The time is 10:41. And we're on the record.

BY MR. GABRIC:

Q. Welcome back, Doctor.

A. Thank you.

Q. I'm going to show you -- let me back up for a second. The Hammond abstracts, Exhibits, I

think it's 1014 and 1015, when did you first become aware of the data reported in these abstracts?

A. Well, I was a person that went to ASCO and ACR every year for many, many years and always attended the antifolate sessions. So I don't know if I went to this or whether I read about it afterward or what. But I certainly was aware of the studies. I can't remember all the posters I went to in the -- in the '90s.

Q. Okay. So can you pinpoint a general time frame when you became aware of this work?

A. I think I was aware of it in the mid '90s, late '90s. Yeah. This was ASCO 1998. I certainly went to that. I know I was there.

And I think this -- the other one was ACR, but I'm not sure. Maybe it was also ASCO. Oh, this is Annals of Oncology. This is from ESMO. I wouldn't have been -- I wouldn't have attended this. I think this is Annals of Oncology supplement, which is, I think, is the ESMO meeting.

Q. Are you referring to Exhibit 1015?

A. Yes. So I likely was there for the 1014, but not for 1015.

Although, actually, I did go to ESMO on more than one occasion during the late '90s, early 2000s. So I'm just not sure.

(Exhibit 1013 incorporated by reference.)

BY MR. GABRIC:

Q. Okay. I'm going to show you what's been marked as Exhibit 1013 in these proceedings. It's a -- the Worzalla paper. I suspect you're familiar with it, Doctor. Right?

Are you familiar with that paper?

A. I am.

Q. This is a paper you cite in your declaration?

A. Yes.

Q. Now go to Page 3236 and there's -- on the left-hand side it says in vitro cytotoxic -- cytotoxicity testing.

Do you see that?

A. I do.

Q. And they're doing a comparison between folinic acid and folic acid. Do you see that?

And to be more complete, on the cytotoxicity activity of LY231514.

A. Right.

Q. What is LY231514?

A. I think that's pemetrexed.

Q. And folinic acid, that's the same thing as leucovorin?

A. That's right.

Q. And based on the data reported here, the leucovorin has a much greater effect on the -- anticancer effect of pemetrexed than folic acid does. Correct?

A. That's right. At least in these cell lines that they tested. Now, it depends on which transporter is present on the cell line. So if you select cell lines that have a lot of reduced folate transport, you get a bigger effect.

Q. And these were cancer cell lines they were testing?

A. These are a variety of cancer cell lines, yeah.

Q. Okay. And so the leucovorin had a greater effect on these cancer cell lines than the folic acid did?

A. Right. Folic acid still had a very substantial effect.

Q. Yeah. But the paper reports here that the folic acid was approximately 100- to

1,000-fold less active than folinic acid at protecting these cancer cells from toxicity. Correct?

A. Would you restate that? I don't see 1,000-fold.

Q. If you go to results.

A. Yes.

Q. And you -- the paragraph, first full paragraph at the end.

A. Yes.

Q. "Folic acid was approximately 100- to 1000-fold less active than folinic acid at protecting cells from LY231514 induced cytotoxicity."

A. Well, it was -- you know, it was in the range of, I would say, 100 to -- I don't see a thousand at all. I just see maybe a hundred. But folic acid reversed it at all, but at higher concentrations.

I think the message is in these cell lines the folic acid was -- required a higher concentration to reverse the antitumor activity.

Right. That's -- that's correct.

Q. Now -- and I think you make reference to this in your declaration -- the tumor cell

line discussed here, this L5178/TK-/HX-, that's a cell line that's especially sensitive to pemetrexed?

A. That's -- it's designed to -- to require the pathway that -- that pemetrexed inhibits. It's not a typical cell line. It's a very disabled cell line. It's a person that's in a wheelchair, basically, if it's a -- a tumor.

Q. And this cell line is especially sensitive to pemetrexed?

A. It's very sensitive, yeah.

Q. And this cell line was injected into the mice?

A. It was implanted in the mice.

Q. Implanted. I'm sorry.

A. Yes.

Q. And so if you look at Figure 2 --

A. Mm-hmm.

Q. -- it shows that mice on a low-fat diet, low fat -- low-folate diet.

A. They should be on a low-fat diet, too.

Q. That would probably be helpful as well.

A. Okay.

Q. On a -- on a low-folate diet. I'm sorry, Doctor.

A. Yes.

MR. PERLMAN: Something you want to tell us?

Q. Let me start over. Strike that.

A. Yes.

Q. In Figure 2, there's some data plotted. Correct?

A. Yes.

Q. Okay. And then we have, it looks like he's plotted some data on the mice who were on the low-folate diet. Right?

A. (Witness nodded.)

Q. Correct?

You have to give a verbal response.

A. Yes, sir.

Q. Thank you.

And he reports here that the mice on the low-folate diet saw 100 percent tumor response at pemetrexed levels of about 0.3 milligrams per kilogram?

A. That's right.

Q. And so this tumor line that was implanted in these mice, that's a tumor line -- a cell line that was especially sensitive to pemetrexed.

A. That's right.

Q. And the data is bearing that out. Correct?

A. That's right. It's quite sensitive. Although I should point out, these are large doses of pemetrexed compared to what a person gets.

Q. Well, you can't quantitatively extrapolate from these numbers and do a human. Isn't that correct?

A. Well, there's a general extrapolation. It's about four. So if you multiply these doses by four --

Q. I have to interrupt you, Doctor. Is that in your declaration?

A. You asked me a question. So I'm answering your question.

Q. Okay.

A. Right? So if you extrapolate --

Q. I'll withdraw the question.

A. If you extrapolate --

Q. I'll withdraw the question.

A. The extrapolation is about four. So it would be roughly equivalent to 4 milligrams per meter squared in people.

Q. Now -- all right.

Now, you were asked in the District Court case down in Indiana about whether you could extrapolate the doses in Worzalla into a human being. Right? Do you recall you were asked those questions?

A. Yes. I might have. I don't remember that.

Q. Let's turn to Page 1262 of your transcript.

(Witness complies.)

Q. And we're going to start on Page 1262 at Line 23. And to give you context, you were being asked about Worzalla. And you let me know when you get there.

A. Got it.

Q. All right. Starting at Line 23 on Page 1262, this is Volume 7.

"QUESTION: Now, you also explained that you tried to extrapolate from the doses here to doses in humans; but I think we talked about earlier that you can qualitatively extrapolate but not quantitatively extrapolate, right?

"ANSWER: That's true. It's an approximation, certainly.

"QUESTION: And you don't actually know how to extrapolate the doses of folic acid from the Worzalla paper to human dose, do you?

"ANSWER: No, no more than I really know how to extrapolate the pemetrexed doses. I mean, they're all approximations."

You give those answers to those questions?

A. I -- I agree. This is an approximation. This is sort of -- this is a rule we use in drug development. It's about a fourfold approximation, but you never can tell. Sometimes it turns out to be 100. And sometimes it turns out to be one.

Q. And you stand by the testimony you gave.

A. Yes, I do.

MR. GROSSMAN: And, Counsel, I'm just going to continue to object to the extent you're trying to read in the record, Dr. Chabner's Cross testimony without introducing his Direct, Redirect testimony. It's incomplete. It's improper. You haven't cured it. We reserve the right to strike all testimony about this.

MR. GABRIC: Your objection is noted, Counsel.

BY MR. GABRIC:

Q. Okay. So we're done with that.

Now, Worzalla is a -- is a preclinical study. Right?

A. Worzalla was a -- was a -- yes, he was a laboratory man.

Q. And the study in Worzalla is a preclinical mouse study?

A. Right.

Q. And mouse models are standard models for preclinical tests for antifolates. Right?

A. For all drugs.

Q. Including antifolates?

A. Yes.

Q. And, in fact, the '209 patent, the patent that brings us here today, talks about mouse studies. Correct?

A. Yes.

Q. And in papers you've authored, you've also referred to mouse studies. Correct?

A. Many.

Q. And in papers you've authored, you've drawn inferences about the results in mouse studies of what you might see in a human being. Correct?

A. Yes.

Q. And that's something one skilled in the art would do in June of 1999. Correct?

A. Oh, yes. We still do it.

Q. Now, do you recall being shown some demonstratives at the trial?

A. I recall being shown a lot of things.

(Worzalla Demonstratives marked Exhibit 1067.)

BY MR. GABRIC:

Q. A lot of stuff. All right. I'm going to represent to you that these are two demonstratives that you were shown during the trial. I've marked them as Deposition Exhibit 1067, actually, it looks like we got a series of demonstratives. They bear slides number -- Slide No. 70, 71, 70- -- I'm sorry, Slide 70, 72, 73, 76, 77.

I'll represent to you that these are some of the demonstratives that you were shown during the trial down in Indiana. I ask you if you recall seeing that information. And to give you context --

A. No, I don't remember.

Q. You don't remember. Okay.

A. No.

Q. To give you context, it was an effort to graph the data reported in the Worzalla paper. Is this ringing a bell at all for you?

A. Pardon?

Q. Is this ringing a bell at all?

A. I think that -- no, it doesn't. But I certainly recognize some of this graph as being from the paper.

Q. Right.

MR. PERLMAN: You're not telling him these were his demonstratives?

MR. GABRIC: No. I'll be -- I'm not trying to confuse anyone. These were Dr. Ratain?

MR. PERLMAN: Ratain.

MR. GABRIC: Ratain. Thank you.

His demonstratives that this witness was cross-examined about at trial.

MR. GROSSMAN: I'm going to object to this exhibit as lacking foundation, lacking authenticity. Dr. Ratain has not offered any testimony here. I believe these exhibits were also incomplete. I believe it was also Dr. Ratain's testimony he referenced issues in terms of the completeness of these documents.

And so we object to them and you need to cure those objections, otherwise we reserve the right to strike all testimony about them.

BY MR. GABRIC:

Q. I just want to focus on Slide 72.

A. Which is Slide 72?

Q. It's at the bottom, right-hand corner.

A. I'm sorry. I don't understand what you mean by "Slide 72."

Q. If you hand me the exhibit, I'll get you to it.

For the record, it's got the number at the bottom, right-hand corner.

A. Where is it?

Q. 72.

A. Oh, okay. Well, basically that's Figure 2.

Q. With -- with some data added. I want to be fair with you, Doctor. I know it's been a couple of years. I'll tell you what it is and you can tell me if you agree or not. Okay?

It's -- I'm trying to avoid misleading you. I'm trying to do you a favor here. All right.

A. You're confusing me, of course.

Q. Yeah. Well, let me -- let me back up.

Okay?

A. All right. I'd prefer to work with these figures. Right? I mean, it's data from this paper.

Q. Well, we can do that. We can start there, then I'm going to go to the slide and ask you to do your best to answer my questions.

A. Okay.

Q. Okay? I really am not trying to confuse you.

All right. So figure 2 --

MR. GROSSMAN: Objection to that representation.

COURT REPORTER: Objection what? I'm sorry.

MR. GROSSMAN: To that representation. But you can go on.

THE WITNESS: Okay.

BY MR. GABRIC:

Q. Well, if I'm confusing you at any time, please let me know.

A. Yes. So I see the figures here. And this is a recreation of multiple figures from the paper. Right? So why don't we work from the paper?

Q. We'll start there. Okay.

A. Okay.

Q. All right. I'm going to try to accommodate you as best I can while still achieving my objectives. All right.

A. I'm trying to give my expert testimony.

Q. I understand. All right. So we're at Figure 2.

A. Okay.

Q. All right.

A. Let's look at that.

Q. We'll start the way you want to start.

A. Good.

Q. Let me make sure I have this figure right. So Figure 2 here is reporting data, we've got the data regarding the low-folate diet mice that's plotted with those little circles that show that there was 100 percent inhibition at about -- starting at about .3 milligrams of pemetrexed. Right?

A. Right.

Q. All right. And then we have those vertical dotted lines. Right?

A. Right.

Q. And that's reporting on what?

A. The lethality in mice in the low-folate diet.

Q. Okay. So as you increase the dose of the pemetrexed in the low-folate diet mice --

A. Mm-hmm.

Q. -- it starts to kill them, as indicated by these vertical lines.

A. Right.

Q. Okay. Now, we have something else plotted here. Right? And it's the low-folate diet mouse -- mice that are supplemented with folic acid. Right?

A. Right.

Q. And that data is plotted with these triangles on kind of the right-hand side of Figure 2. Right?

A. Right.

Q. And it shows that you start seeing a tumor inhibition at about 3 milligrams per kilogram and, as you dose up to 30 milligrams per kilogram, you get 100 percent inhibition. Right?

A. Right.

Q. Okay. Now, Worzalla also looked at standard diet mice. Correct?

A. Right.

Q. And he has data in his paper about the standard diet mice. Correct?

A. It's not really a standard diet. It's a relatively high-folate diet. It's not what we would consider a standard diet.

Q. Thank you, Doctor. A standard diet for a mouse.

A. That's right. Exactly.

Q. But he didn't plot that data in Figure 2. Right?

A. Right.

Q. Okay. Slide 72 plots that data, overlies that data on the Figure 2. That is what Slide 72 is.

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. And my question is: Do you agree that that data for the standard diet is --

A. I don't know what the --

Q. -- is accurately plotted?

A. I don't know what these lines. Are you talking about these lines (indicating)?

Q. Yeah. The blue. In blue on the demonstrative is a standard diet data that's

plotted overlaid on the Figure 2 of Worzalla.

A. Where did this data come from?

Q. From Worzalla. It's in Worzalla.

A. No. Where?

Q. Why don't we go to --

A. Standard diet.

Q. -- Page 3237. Starting at, on the left-hand side, about four lines up from the bottom, he says, "the antitumor dose response with folate supplementation was virtually identical to that observed for mice receiving standard diet."

Do you see that?

A. I don't -- oh.

Q. You're nodding your head.

A. I do see it. I see it. Yeah. Right.

Q. And then he goes on to say, "However, the lethality was significantly greater for mice on standard diet, parenthetical lethality at 400 and 800 milligrams per kilograms per day of 10 percent, 100 percent respectively."

Do you see that?

A. Mm-hmm.

Q. All right. So the lethality, if you look at our demonstrative 72 is the blue vertical

lines for standard.

A. Oh, I gotcha. I gotcha. Right.

Q. So that's plotted correctly. Right?

A. Yes.

Q. So at 400 milligrams we have 10 percent lethality for the standard diet mice.

A. And a hundred.

Q. And at 800 milligrams, the second vertical line on Slide 72 --

A. Right.

Q. -- we have 100 percent.

A. Right.

Q. So Slide 72 is accurate in reporting that data. Correct?

MR. GROSSMAN: Objection to the form of the question.

BY MR. GABRIC:

Q. If you have a problem with it --

A. No. I don't have a problem with it.

Q. Okay. And in Table 2, Worzalla reports a percent tumor inhibition.

MR. PERLMAN: I think you mean Table 2.

BY MR. GABRIC:

Q. Table 2.

A. Yeah.

Q. And it reports 90 percent inhibition at 10 milligrams and 100 percent inhibition at 30 and 100 milligrams.

A. In this disabled tumor, right.

Q. And that's the standard diet mouse that's plotted on Slide 72.

A. Right. Where is that?

Q. We've got the data accurate.

A. Yes, I see.

Q. Okay. So you're comfortable that we've accurately overlied the standard diet data in Worzalla --

A. Yes.

Q. -- on to Figure 2?

MR. GROSSMAN: Objection to the form of the question.

A. Yes. I understand what you're doing. Okay.

Q. Okay. If you have any problems with it, I want to hear about it.

A. Okay. Go ahead.

Q. Have I got it right?

A. We'll talk about the problems when you get to it.

Q. But we plotted the data correctly?

A. Yes.

Q. We got that far.

A. Yes. You did get that far. Okay.

Q. That's a start.

All right. Now, the Worzalla paper draws some conclusions. And I want to explore those for a second. If you look at Page 3238 and you're -- I see you're writing on my exhibit.

A. A new graph. I'm just figuring your graph. Okay.

Q. Well, I can't stop you, I don't think, from writing on my exhibit.

A. All right.

MR. PERLMAN: Do you want a clean copy for the record?

MR. GABRIC: I don't know what I'm concerned about.

THE WITNESS: Let's go.

MR. GABRIC: We'll just keep going.

MR. PERLMAN: We can work that out, if that is what your concern is.

MR. GABRIC: Just to be candid, I just want him to answer my questions. Thanks.

MR. PERLMAN: I think the writing is probably helpful.

MR. GABRIC: Okay.

BY MR. GABRIC:

Q. All right. So we're on Page 3238 of Worzalla.

A. Okay.

Q. And in the --

A. 3238. Yes.

Q. Are you with me? I'm on the right-hand side.

A. Okay.

Q. All right. And Worzalla says, about -- it's the middle paragraph --

A. Yes.

Q. -- about one, two, three -- about seven lines up from the bottom, "However, low-folate diet animals with high levels of folate supplementation demonstrated decreased lethality to LY231514 compared to conventional diet animals."

Do you see that?

A. I do.

Q. That's a standard diet mice.

A. I do.

Q. And the data supports that conclusion. Correct?

A. It supports it in mice. Yes. And I should point out that there's a significant problem in trying to bring this data to humans. I don't know if you want to talk about that, we can --

Q. I want to just get you to answer my questions.

A. Okay.

Q. If your counsel wants to ask you questions about that, I can't stop him. He's free to do so.

A. Okay. I would just say that -- that this is based on the idea that you could potentially give such a high dose to people. It is an astronomical dose. Mice tend to tolerate drugs, particularly drugs that require renal excretion, much better than humans. In order to get this, you'd to use a dose in humans which would be extraordinary. Okay. That is my little speech.

Q. Okay. Fine. And then, after he draws this conclusion that we discussed --

A. Mm-hmm.

Q. -- he says that this -- he says, I'll quote him, suggesting that -- so let me read the

whole thing.

"So low-folate diet animals with high levels of folate supplementation demonstrated decreased lethality to LY231514 compared to conventional diet animals," then comma, "suggesting that folate intake can be manipulated to achieve greater therapeutic effects."

Right? That's his conclusion?

A. That's his conclusion.

Q. And then further down, based on this data, the last line of -- on Page 3238, bridging on to 3239, he says, "The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity."

That's what he says. Right?

A. Yes.

Q. And he's talking about human beings. Right?

MR. GROSSMAN: Objection to the form of the question.

A. It says "may." Possibly. Yes. It would depend on trials.

BY MR. GABRIC:

Q. And he's referring to human beings at this point, not mice?

A. Yeah. Might. Yeah.

Q. Do you know when you became aware of the Worzalla paper?

A. No.

Q. No?

A. No.

Q. Was it in connection with your engagement in the Lilly litigation with Teva?

A. It might -- I really don't know. I can't answer that question. I mean, this is my field. So I very well might have read it. But I don't know.

Q. You can't pinpoint?

A. No.

Q. Let's show you what we've marked as Exhibit 1068.

(Document Bates-stamped DPEM2_0002317 through -2322 marked Exhibit 1068.)

MR. GROSSMAN: Do you have a copy for counsel?

MR. PERLMAN: Or just tell us what it is.

MR. GABRIC: It's the Worzalla abstract.

BY MR. GABRIC:

Q. And before we leave Worzalla and looking at the Slide 72 with the standard diet overlied --

A. What page are you looking at?

Q. I'm going back to Slide 72. I'm going in reverse for a second.

A. I'm sorry.

Q. That's okay.

The Slide 72, the low-folate -- the low-folate diet plus folic acid mice, there was no toxicity or no lethality from pemetrexed regardless of dose with respect to those mice on the folic acid supplementation?

A. Hold on just a minute. Let me just look at it.

MR. GROSSMAN: Objection to the form of the question.

A. Okay. Ah. Interesting.

BY MR. GABRIC:

Q. To help you out, I'm comparing the blue to the red. The standard diet to the low-folate diet plus folic acid.

Do you see that?

A. The blue to the red. Okay.

Q. All right. And you're on Slide 72?

A. (Indicating).

Q. Yes, you are.

And so in the standard diet compared to the low-folate diet with folic acid supplementation for about 10 milligrams pemetrexed on, the efficacy is pretty much the same between those two. Fair?

MR. GROSSMAN: Objection to the form of the question.

A. This is really a weird experiment. How could you possibly measure percent inhibition if you're killing all the mice?

BY MR. GABRIC:

Q. I'm just asking you about the data.

A. I think that -- the data actually, now that I look at it, doesn't make a lot of sense.

One other thing that's missing in this data is this point (indicating). So that it shows that the band of activity for the low-folate diet is pretty broad and he basically left that point out. It's in his table, but he didn't put it in here (indicating). And so I think, personally, what he's done -- my conclusion is you shift the dose response curve over to the right but you're

not really making much -- much headway until you get to very high doses of pemetrexed, which are intolerable in people, because they would be massive doses.

Q. Worzalla doesn't report that. Right?

A. He -- this is left out of his -- his table -- or his figure. And I don't know why he left it out. He made it look better, maybe.

Q. We're going --

A. But also this whole thing about percent inhibition and percent lethality, how could you have 100 percent inhibition if you've killed all the mice? Of course, you have, because they're all dead --

Q. Well, Doctor, the mice, the low-folate diet mice with folic acid pretreatment, you couldn't kill them. They aren't dead.

A. Well, but these are, the ones that he's comparing them to, the standard diet are.

Q. Right. Right. So the ones on the standard diet without folic acid supplementation, they start dying at 800 milligrams but with folic acid supplementation, they don't die. Right?

A. My point is how could you -- how could you determine percent inhibition in mice that are

dead?

The way you present -- you determine percent inhibition is usually by looking at lifespan, and you can calculate how much -- how much of the tumor you've killed. Let's see -- let's see how he does it. I'd like to see how he does it.

Yeah. He's measuring tumor dimensions. He says here, "No group was included in the sample for therapeutic analysis in which death attributed to drug toxicity exceeded 20 percent of the treated group." Here we've got data for the blue and -- the blue curves, we have data for animals -- oh, I guess he doesn't give actually data there. He doesn't. He doesn't give any data, because he's at a lethal dose. Okay. Now I understand this.

Q. Okay. Are we ready to move on?

A. Yes.

Q. Okay.

A. Okay.

Q. I gave you that Exhibit 1068. This is the Worzalla abstract.

A. Yes.

Q. Okay. And I believe this was shown to you at the trial in Indiana.

Do you recall seeing this document?

A. Yes.

Q. All right. And is this just a shorter version of the Worzalla paper, basically?

MR. GROSSMAN: Objection.

A. Yes.

BY MR. GABRIC:

Q. And he draws a conclusion based on a comparison of the time frame, I'm sorry -- he draws a -- let me start over.

In Worzalla abstract, he draws a conclusion based on the comparison of the standard diet mice versus the low-folate diet mice with folic acid supplementation at the bottom.

Do you see that?

A. Yes.

Q. Okay. And he points out for mice on SD -- that's standard diet, right?

A. (Witness nodded.)

Q. Is that correct?

A. Right.

Q. Comma, MTA -- that's pemetrexed?

A. Where? I see. I'm having a hard time following you.

Q. I'm sorry. Abstract 3198.

A. Okay. Got it.

Q. So for mice on standard diet, SD?

A. Got it.

Q. Comma, MTA, that's pemetrexed. Right?

A. Mm-hmm.

Q. Produced greater than 95 percent inhibition of tumor growth at 30 to 300 milligrams per kilogram.

A. Mm-hmm.

Q. But all mice died at 800 milligrams per kilogram. Right?

A. Right.

Q. That's what he says.

And that's what one of ordinary skill in the art would understand in June of 1999. Right?

A. Mm-hmm.

Q. I'm sorry. You've got to -- you have to verbally respond.

A. Yes. I see.

Q. Okay.

MR. PERLMAN: Doctor, let me make a suggestion. Let him finish the question, leave out the intermediate mm-hmms. And then at the end, give him an answer.

THE WITNESS: Okay.

MR. PERLMAN: I think it's going to be more helpful for all of us.

BY MR. GABRIC:

Q. Then he goes on and he says for mice on low-folate diet supplementation, p.o., was that by gavage?

A. Per os.

Q. What's that mean?

A. Mouth.

Q. Okay.

A. Gavage.

Q. Okay. Gavage.

With 15 milligrams per kilogram daily folic acid, 100 percent tumor inhibition was seen from 30 to 100 milligrams [sic] per kilogram with no lethality.

A. 30 to 1000.

Q. I'm sorry. 30 to 1000. Thank you, Doctor.

That's what he reports to one of ordinary skill in the art in June of 1999. Right?

A. Yes.

Q. And then he also reports to one of ordinary skill in the art, thus, addition of oral folic acid did not reduce antitumor activity of

MTA, but did lessen toxicity. Correct?

A. Yes. That's what he says.

Q. And he drew that conclusion based on comparing the data for the standard diet mice versus the low-folate diet mice with folic acid supplementation. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Yes.

BY MR. GABRIC:

Q. And so this conclusion that is reported in the Worzalla abstract tells one of ordinary skill in the art, in June of 1999, that based on the comparison of the standard diet in the low-folate diet mice, plus folic acid, addition of oral folic acid did not reduce antitumor activity of pemetrexed, but did lessen its toxicity. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. I wouldn't agree with that blanket statement. That's maybe his conclusion in the last sentence, but my conclusion from this would be in this extraordinarily disabled tumor, which is hypersensitive to pemetrexed, that one can

manipulate the dose of folic acid, very high dose of folic acid to reverse activity of extremely high doses of pemetrexed. That's my conclusion. That was the experiment.

BY MR. GABRIC:

Q. Now, turn to Page 1260 of your trial testimony. And I direct you to Line 21.

(Witness complies.)

Q. Are you there?

A. Yes.

Q. Okay. And you were asked about the abstract, the Worzalla abstract, and starting at Line 21:

"QUESTION: And then based on that comparison of the standard diet and the low-folate diet plus folic acid, they conclude, 'Thus, addition of oral folic acid did not reduce antitumor activity of pemetrexed but did lessen toxicity,' right?

"ANSWER: That was their conclusion. It might not have been my conclusion.

"QUESTION: It was a reasonable conclusion for them to draw, right?

"ANSWER: I think that was their conclusion, yes."

Did you give those answers to those questions?

A. I gave the exact answer this time. It was their conclusion. It applies to the specific experiment they did. And they drew that conclusion based on the experiment with the extraordinarily disabled mice in doses which are unachievable in people.

Q. And you stand by that trial testimony. Right?

A. Yes. I stand by my testimony.

Q. There's something we call the Niyikiza or Niyikize --

A. Niyikiza.

Q. -- abstracts. And --

MR. GABRIC: Here you go. I've got too many papers here. I'll give this to you in a second, Doctor.

A. Okay.

MR. GABRIC: I show you the first one. It's Exhibit 1006.

(Exhibit 1006 incorporated by reference.)

MR. GABRIC: And then the other one is Exhibit 1016.

(Exhibit 1016 incorporated by reference.)

MR. GABRIC: I'll just lay it next to your water.

BY MR. GABRIC:

Q. Now, do you know Mr. Niyikiza?

A. Pardon?

Q. Do you know Mr. Niyikiza personally?

A. Yes. It's Dr. Niyikiza.

Q. Dr. Niyikiza.

A. Yes.

Q. You know him personally?

A. Yes.

Q. Is he a friend of yours?

A. I would say he's an acquaintance.

Q. And not to -- not to peel too many layers away, what do you mean by "acquaintance" versus a "friend"?

A. I mean, I know him.

Q. Okay.

A. He's not one of my personal -- close personal friends.

Q. Okay. When did you first meet Dr. Niyikiza?

A. Oh, probably, I don't know, 15 years

ago, maybe 20 years ago. I'm not sure.

Q. Do you currently work with Dr. Niyikiza on anything?

A. I'm friendly with him. He comes and visits me in Boston. I'm not formally associated with him on anything yet.

Q. You're not working for him or doing any work for any of his companies?

A. No. I've talked to him many times, though.

Q. Were you -- I'm sorry if I already asked this. When did you first meet Dr. Niyikiza? About what time frame?

A. I said maybe 15, 20 years ago. I'm not sure.

Q. Okay. Now, was there a time that you were on the scientific board for a company called Merrimack Pharmaceuticals?

A. Yes.

Q. Are you still on that board?

A. No.

Q. Okay. What time frame were you on the board with Merrimack?

A. Oh, God. I don't know. Maybe six, seven years ago. Maybe for a couple of years.

Q. All right. And did Dr. Niyikiza invite you to participate on the board of directors?

A. I don't know if he invited me. I knew the -- the CEO and they asked me. Yeah.

Q. And at the time you were on the board of directors of Merrimack, Dr. Niyikiza --

A. I wasn't on the board of directors.

Q. I'm sorry.

You were on the scientific advisory board.

A. I was on a scientific advisory board.

Q. Okay.

A. Yeah.

Q. And at the time you were on the advisory board, was Dr. Niyikiza an executive?

A. He also worked there. Yes.

Q. Okay. Do you know where Dr. Niyikiza works now?

A. He's in Philadelphia. I don't know where he -- his office is.

Q. Do you know who he works for?

A. I think he works for himself.

Q. Does he have a company?

A. I think -- you know, I don't know the formal, the situation whether it's a company or not.

Q. Okay. Have you spoken to Dr. Niyikiza about any of the -- these matters involving the '209 patent?

A. Oh, I think I did. You know, when the trial was going on, yeah. Not -- not since then.

Q. That's the trial in Indiana?

A. Yeah.

Q. Now, these Niyikiza abstracts, when did you first become aware of this information?

A. You know, that would be very hard for me to say. I certainly became intimately aware of it with this trial. But I was aware -- you know, I was obviously aware of the regimen that was being used and why, for many years.

Q. Can you pinpoint when you became aware of the data in the -- reported in Niyikiza?

A. No, I can't. I'm sorry.

Q. Now, I want to focus on Exhibit 1016. And the Niyikiza reports with respect to -- well, let's back up.

MR. GROSSMAN: I just want to make sure you're looking at the right one.

MR. GABRIC: Yeah.

MR. GROSSMAN: I think there's two.

A. 916 is right here.

MR. GROSSMAN: Yeah. This is a separate exhibit (indicating).

BY MR. GABRIC:

Q. So are you on Exhibit 1016?

A. Yes.

Q. And he reports, I'm kind of in the middle. "There was a strong correlation between baseline homocysteine levels and the development of the following toxicities," and he goes on.

Do you see that?

A. I do see it.

Q. All right. So he's -- he's reporting here on a correlation between homocysteine levels and toxicity experienced with the -- with pemetrexed. Correct?

A. That's right.

Q. And he also looked at MMA levels. Correct?

A. Yes.

Q. And he reported that he didn't see any correlation with respect to MMA. Right?

A. That's right.

Q. He didn't say there wasn't -- there was no correlation. Correct?

A. Well, no. He said that he didn't see a

correlation.

Q. Right. And, in fact, some of the other things he was looking at when there was no correlation, he said so. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. He says no correlation between toxicity and the remaining prespecified predictors were -- was seen. And the other -- among those predictors were MMAs. So no correlation was seen.

BY MR. GABRIC:

Q. Right. And before that, he basically says, I think it's cystathionine.

A. Cystathionine. Right.

Q. He said with respect to cystathionine levels, there was no correlation. They did not correlate. Right?

MR. GROSSMAN: Objection to the form of the question.

A. Well, I don't -- I don't think that's a very important distinction to say it was not seen versus there was no correlation. I mean, you know, with either one, if you looked at 10,000 patients, you might have seen a correlation.

Q. Right. But one of ordinary skill in the art in June of 1999, reading this document, would understand that with respect to cystathionine levels, Niyikiza reports that they did not correlate. Correct?

MR. GROSSMAN: Objection. Asked and answered.

A. Yes.

BY MR. GABRIC:

Q. And with respect to MMA levels, one of ordinary skill in the art would understand that he just didn't see a correlation. Correct?

A. No. The reason there's a difference in the way he phrased it, because cystathionine levels did correlate with fatigue, so it's a different sentence structure, but the intent is the same.

Q. Well --

A. I mean, I don't know. I majored in history. I was an English-proficient person. I can see why he constructed the sentences differently. Maybe that's not obvious to you.

Q. Well, I just want to understand that.

So it's your opinion, one of ordinary skill in the art, in June of 1999 that when

Dr. Niyikiza reports that no correlation with MMA was seen, that what he really meant was none exists? Is that your opinion?

A. No. You couldn't say that about anything. Nothing was seen in this study. And the same thing is true of cystathionine. Nothing -- it wasn't seen in this study. The point I'm trying to make is that neither one is an absolute statement about whether it exists in nature if you did a large enough study. You can't ever -- scientifically you can't exclude something that way. All you can say is I didn't see it in the study.

Q. And Dr. Niyikiza reports with respect to cystathionine levels, he comes out and says it, they did not correlate. Correct?

MR. GROSSMAN: Objection. Asked and answered.

A. I've tried to explain my answer. I think any reasonable person would interpret this as saying the data in this study does not support a correlation for either cystathionine or MMA with the usual toxicities, neutropenia, thrombocytopenia. It doesn't mean that they don't exist. Either one could exist, but in this

study they didn't find it.

Q. I just want to make sure I understand your opinion. In your opinion, one skilled in the art would interpret Niyikiza to --

A. Well, I'm sorry. Go ahead.

Q. Would interpret "does not correlate" in the same way as "none was seen"? No correlation.

A. Absolutely.

Q. Okay. I just want to make sure I understand your opinion.

Now, you would agree that one skilled in the art in June of 1999 reading the Niyikiza abstract would understand that there could be a correlation, just none was seen?

A. Yes.

Q. And one skilled in the art would have understood that there just may not have been enough people in the study to observe the correlation?

A. That's right.

Q. And with respect to cystathionine, Dr. Niyikiza affirmatively says, cystathionine levels did not correlate with toxicity. Correct?

A. Well, that's not of --

MR. GROSSMAN: Objection. Asked and

answered.

A. I don't think that's an affirmative statement. That's a negative statement. It says there was no correlation in this data.

BY MR. GABRIC:

Q. So let's go to Page 1303 of your trial testimony. And we go to Line -- I'll let you go get to Page 1303.

(Witness complies.)

Q. Go to Line 19.

A. Yes.

Q. You were asked the following question with respect to Niyikiza:

"QUESTION: They affirmatively say here" -- I'm sorry. "They affirmatively say here -- the Niyikiza abstract affirmatively says here, cystathionine levels did not correlate with these toxicities, right?

"ANSWER: That's right."

Did you give that testimony?

A. You've avoided my prior testimony, which says, "Is this an affirmative statement?"

I said, "No, it's in sort of a double negative. It's not an affirmative, in the sense of me saying yes."

But the statement is -- stands as it is. I didn't -- I didn't object to the statement, no.

Q. You're referring to some prior testimony. So you were asked the follow-up question.

A. One second before.

Q. Right.

A. Same answer. You asked me if it was an affirmative statement. Here I say, It's a double-negative statement, it's not affirmative.

But then the guy asked me again, Well, did he say that?

And I said, Yes, he did say that.

Q. So you stand by this testimony. Right?

A. Yeah.

Q. Yeah. Okay.

And concerning the other things that were tested for, including MMA, there's a different statement. Correct? There's no correlation?

A. There's a second statement I wouldn't say different.

Q. Why don't we go to Page 1303, where we just were.

(Witness complies.)

Q. Starting at Line 23.

A. What page?

Q. Page 1303. Line 23.

A. Okay.

Q. Question, starting at line 23:

"QUESTION: And concerning the other statements that were measured" -- I'm sorry.

"And concerning the other things that were measured, there's a different statement. It's just that the correlation was not seen, right?

"ANSWER: Yeah."

Did you give that testimony?

A. It is a different statement. It's another statement. I don't know what you mean by the word "different."

Would you explain that to me and maybe I can answer it. It is a different statement, it's a second statement.

Q. I don't think we're arguing at this point. I think we're fine. I'll move on.

A. Well, it wasn't clear to me what you were after.

Q. Are you an expert in multivariable analysis?

A. I know what it is.

Q. Do you consider yourself an expert?

A. I'm not a statistician. No.

Q. Now, Niyikiza reports that he was seeing a correlation between toxicity and baseline homocysteine levels at about, it was ten micromolar?

A. That's right.

Q. Okay. Is that within the normal range of homocysteine levels?

A. It's variable.

Q. Is it -- would you consider ten to be within the normal? I understand --

A. It's high normal.

Q. High normal?

A. Yes.

Q. Would one of ordinary skill in the art in June of 1999 understand that?

A. I suppose if they were a medical oncologist and they used home -- or hematologist and they were measuring homocysteine, they might. Or a cardiologist. Not all doctors measure homocysteine levels very frequently. It's sort of an esoteric thing.

Q. And I'm just trying to understand, would one of ordinary skill in the art in June of

1999 understand that ten micromolar is high normal for homocysteine?

A. Yes.

MR. GROSSMAN: Ralph, you're moving on to another topic?

MR. GABRIC: Yeah. That's fine. I was going to ask for one anyway.

MR. GROSSMAN: Okay.

THE VIDEOGRAPHER: The time is 11:40, and we're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: Here begins Disk 4 in the deposition of Bruce Chabner, M.D. The time is 11:54. We're back on the record.

BY MR. GABRIC:

Q. Welcome back, Doctor. I'm going to show you what is Exhibit 1007 in these proceedings. It's the Calvert paper.

(Exhibit 1007 incorporated by reference.)

BY MR. GABRIC:

Q. And you talk about this paper in your declaration, but --

A. Yes.

Q. Okay. I just have a few questions

about it.

When did you become aware of this paper?

A. Well, I'm very fond of Hilary Calvert. I know him well. I like everybody named Hillary.

Q. Sorry.

A. What else can I say?

All right. So, I've known him a long time.

Q. When did you first become aware of this paper?

A. Oh, I think I probably read it years ago.

Q. Can you pinpoint what time frame?

A. No, I really can't. No.

Q. And I want to turn to Page 8 of Dr. Calvert's paper.

A. Okay. Page 8.

Q. Yeah. It's on the upper left-hand.

A. Yeah. I got it. I got it. I got it. Yeah.

Q. And Dr. Calvert states -- I'm on the right-hand side, right-hand column.

A. Mm-hmm.

Q. Starts -- the sentence that starts at the bottom "thus." Do you see that "thus"?

A. Yes, I see it.

Q. And he makes the following statement: "Thus, any functional deficiency either in B12 or folate will result in reduction in the flux through the methionine..."

A. Methionine.

Q. Methionine?

A. Methionine.

Q. Methionine?

A. -neen. Yeah.

Q. Thank you.

"...through the methionine synthase in a consequent increase in the plasma level of homocysteine."

Do you see that?

A. I do.

Q. And the functional deficiency that Dr. Calvert is referring to is a deficiency in functional folate as opposed to folic acid. Correct?

MR. GROSSMAN: Object to the form of the question.

A. Wait. I'm not sure what you asked. Please restate it.

BY MR. GABRIC:

Q. The functional deficiency in folate

that Dr. Calvert is referring to here on Page 8, he's talking about a deficiency in functional folate, not folic acid. Correct?

MR. GROSSMAN: Same objection.

A. Well, they're related. I mean, in the sense that if you have a folic acid deficient diet, you're going to have a deficiency in functional folate.

Q. And he's referring to functional folate, a deficiency in functional folate in this passage. Correct?

A. Yeah. I'm not exactly sure what he means by that. I think he means that a deficiency that affects the various aspects of folic acid metabolism in people.

Q. Can you pull out your trial testimony?

A. Yeah.

Q. We'll go to Page 1299.

(Witness complies.)

A. Mm-hmm.

Q. And starting at Page -- I'm sorry, Line 20 --

A. Yes.

Q. -- and this is in reference to the Calvert paper:

"QUESTION: He talks about, 'Thus, any functional deficiency, either in B12 or folate, will result in reduction in the flux through the...'" -- how do you pronounce that again?

A. Methionine.

Q. Methionine. I'm going to have a problem with that one.

"'...methionine synthase and consequent increase in plasma level and homocysteine,' right?"

A. Mm-hmm.

"ANSWER: Right.

"QUESTION: And there he's talking about the functional folates as you were talking about earlier, not folic acid, right?

"ANSWER: Well, it says functional deficiency either in B12 or folate, yeah.

"QUESTION: When you have a functional deficiency, you're talking about a deficiency in the functional folate?"

"ANSWER: The folate. Right."

Did you give those answers to those questions?

A. Yeah.

Q. And you stand by that testimony.

Right?

A. Well, yeah. I suppose, I'm not sure exactly what it means, but I do stand by it.

Q. And that's how one of ordinary skill in the art in June of 1999 would interpret that passage in Calvert. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. I wish you would actually state what you're trying to say about folate deficiency, functional deficiency. What -- what is it you're trying to say?

Q. Doctor, I get to ask the questions here.

A. Yeah. But I'm afraid I don't -- I'm not fully understanding your point here.

Q. Now, on Page 8, Dr. Calvert notes that a functional folate deficiency can result from not having enough Vitamin B12. Correct?

A. Yeah. It's a functional deficiency in the reduced folate pool. Yes.

Q. And the functional deficiency in the reduced folate pool can cause homocysteine levels to go up. Correct?

A. Yes. That's right.

Q. And then on Page 9, Dr. Calvert --

A. Actually, it's a deficiency of 5-methyltetrahydrofolate. That's the required cofactor.

Q. And that deficiency -- I'm sorry.

Now, on Page 9, the next page of the paper, at the very top below the figure, Dr. Calvert reports "the measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA."

Do you see that?

A. I do.

Q. And MTA is pemetrexed?

A. Yes.

Q. And he cites to Footnote 17. And that's -- that's one of the Niyikiza abstracts we talked about earlier. Correct?

A. That's right.

Q. And thus Dr. Calvert, in his paper, is suggesting to a person of ordinary skill in the art, as of June of 1999, that a deficiency in either functional folate or B12 could result in high levels of homocysteine. Right?

A. Right.

Q. And so the -- now, the Figure 8

illustration, do you understand what Dr. Calvert is trying to convey to a person of ordinary skill in the art in 1999, what he's trying to illustrate here?

A. Yes.

Q. What is he trying to illustrate?

A. Which figure are you talking about?

Q. I'm sorry. Let me ask you a different way.

What would Figure 8 on Page 9 --

A. Yes.

Q. Okay. What is -- what is this figure telling one of ordinary skill in the art in June of 1999?

A. The reduction in the pool of 5-methyltetrahydrofolate will impair methionine synthesis. And it will lead -- well, that's fine.

Q. And that leads to elevated homocysteine levels?

A. Yes.

Q. And do you -- is this an accurate illustration?

A. Yes.

Q. And this Figure 8 also illustrates to

one of ordinary skill in the art that a B12 deficiency can also result in increased homocysteine levels. Correct?

A. That's right.

Q. And that's how one of ordinary skill in the art would understand this diagram --

A. Yes.

Q. -- in June 1999?

A. Yes.

Q. I'm going to show -- I'm done with that one, Doctor.

I'm going to show you what are Lilly Exhibits -- I'm sorry, 2063 and 2064.

(Exhibit 2063 incorporated by reference.)

(Exhibit 2064 incorporated by reference.)

BY MR. GABRIC:

Q. And these are the Zervos -- is that how you pronounce it?

A. Zervos.

Q. Zervos abstract.

A. It's a Greek name, yeah.

Q. I figured out that much.

And you cite these abstracts in your

declaration.

You've seen these abstracts before?

A. I do see the abstract, yes.

Q. You're familiar with these abstracts?

A. Yes.

Q. You cite them in your declaration?

A. I cited them.

Q. And these are from 1997 time frame?

A. Yes. September 1997.

Q. Okay. So these are before the Niyikiza abstracts. Correct?

A. Yes.

Q. So we'll just -- I'll go with 2063 for now.

Does Doctor, I don't know if he's a doctor, I'm assuming so, does the Zervos abstract report to one of ordinary skill in the art how elevated homocysteine levels had to be to be -- well, let me strike that.

Does he explain what he means by folate deficiency in here to one of ordinary skill in the art?

A. No. He just says that the elevated homocysteine and cystathionine in normal MMA levels. That's the way -- I guess that's his

definition of it.

Q. So we don't know what the homocysteine levels were?

A. No.

Q. So we don't know if they were high, normal or --

A. No.

Q. And the study of 2063 involved 116 patients. Is that correct? I'm sorry.

A. 118.

Q. 118.

Now, he doesn't state -- well, I guess he's -- he's observing, what, 11 patients that he's identified as folate deficient under some definition he hasn't reported?

A. He said that there were 11 patients that had high homocysteine and high cystathionine and normal MMA.

Q. Okay. And so he's looking at 11 patients that had high homocysteine and normal MMA but he hasn't defined what those homocysteine and MMA levels are. Correct?

A. He hasn't given you the data.

Q. Okay. And does he address whether there's any toxicity in the other, what, 107

patients that he did not label as folate deficient?

A. No, not in this abstract. No.

Q. So we don't know how many, if any, of these other patients manifested toxicity?

A. That's right.

Q. And we certainly don't know the MMA levels and the homocysteine levels of those other 107 or so patients?

A. Right.

Q. Now, Doctor -- or the Zervos abstract, Exhibit 2063, at the very bottom, reports -- the last three lines -- "from this data, we would conclude that functional folate status may be a reliable prognostic indicator of hematologic toxicity in patients treated with LY231514."

A. Mm-hmm.

Q. Do you see that?

A. Yes.

Q. And that's pemetrexed?

A. That's right.

Q. And that's how one of ordinary skill in the art would understand him to be reporting in June of 1999?

A. Right.

Q. And one of ordinary skill in the art would understand -- he further says that "further investigation is warranted to support this conclusion." Correct?

A. Right.

Q. And take the time you need, but Exhibits 2063 and 2064, I think the number of patients tested was 118 versus 116, but the substance is generally -- the study is generally the same?

A. Mm-hmm. Yes.

Q. Yeah.

A. Although one has 11 patients who had functional folate deficiency, however he defines it, and the other one only had 8.

Q. And correct me if I'm wrong, but one of ordinary skill in the art would understand that he did two -- two studies that were similarly structured?

A. Yes.

Q. That's --

A. This study came after this study (indicating).

Q. Okay. Which one came after? What exhibit?

A. The one with 118 patients.

Q. Okay. So he did a first study with 116 patients?

A. Then he added two patients.

Q. He added two more?

A. Well, that's 116 and 118.

Q. Okay. So it's cumulative. He just did two more --

A. Yes. That's right.

Q. -- and updated his work?

A. That's right.

Q. That's what I was trying to understand. And one of ordinary skill in the art, that would be their understanding in June of 1999?

A. Yes.

MR. GABRIC: I show you what's been marked as Exhibit 1028.

(Exhibit 1028 incorporated by reference.)

BY MR. GABRIC:

Q. And for the record, this is the Tisman abstract. In the upper right-hand corner.

A. Got it.

Q. Okay. And this is an abstract you cite in your declaration. Correct?

A. Right.

Q. This abstract reports on the study involving -- I'm going to ask your help. 5-dash --

A. What, 5-fluorouracil. 5-fluorouracil.

Q. Thank you.

A. We call it "5-FU" for short.

Q. 5-FU. Okay.

A. 5-FU.

Q. All right.

A. It makes it easier.

Q. The neighborhood I hang out, "FU" has a different meaning.

A. I know. Unfortunate. It's got a five in front of it. That's important.

Q. It's an important five.

MR. GROSSMAN: Try to keep things clean here.

MR. GABRIC: I'm just trying to keep it light.

BY MR. GABRIC:

Q. Would one of ordinary skill in the art -- my colleague just pointed out to me there's two Tisman abstracts on this page.

A. Yes.

Q. And I want to focus on the one in the middle on the right-hand side.

A. Got it.

Q. Okay. We're on the same page?

A. I got it.

Q. Okay. Now, would one of ordinary skill in the art in June 1999 understand that 5-FU was a TS inhibitor?

A. Yes. It's a very different TS inhibitor than the antifolates.

Q. But a TS inhibitor, nonetheless?

A. Yes.

Q. And you don't -- it's your view that 5-FU is not an antifolate. Correct?

A. It isn't. It's a pro-folate. Because it requires folic acid to bind to its target. And I've been very involved in this research. And I write chapters about it. I'd be happy to explain it. But it's very different than the antifolates, which they bind to a separate site and compete with the folate.

Q. And do you have an understanding of -- actually, the '209 patent, actually, I believe refers to 5-FU as an antifolate, though.

A. Yes. That's unfortunate because

they -- I don't know who wrote the patent, but they apparently didn't understand what it was.

Q. Okay. So that's -- that was incorrect in the patent.

A. Yes. I think a person of ordinary skill would recognize 5-FU is not an antifolate. If you look at textbooks of pharmacology, it's always -- it's considered in a separate chapter. It's a pyrimidine antagonist.

Q. And if I understand your opinion from your declaration, it's your view that one of ordinary skill in the art in June of 1999 would not find this Tisman reference particularly relevant because of discoveries that took place between 1985 and 1999 regarding how the folate pathway works?

A. Well, this requires a little dissertation, I guess, if you want to go through that. But in the early 1980s, a woman in Hakala, at Buffalo, Roswell Park, showed that she could enhance 5-FU activity by adding folates.

And the reason for that is something that I work on a lot and that is that the very tight binding of 5-FU to its target, thymidylate synthase, requires a reduced folate cofactor. It

actually requires a folate. And when you give a folate to a patient, you get a better response, because you're allowing the anti-pyrimidine to bind to its active site and form -- it's a very tight complex. It's in some circumstance, irreversible complex.

And that's very different than the way the antifolates work at that site, at TS. The antifolates work by competing with the folic acid cofactor from binding to the -- to the site. So the physiologic reaction is a folate becomes the donor to uracil and a folate is required for activity and the antifolates interrupt that.

With 5-FU, the anti -- the folates, the physiologic folates, are required for the binding of 5-FU. In the absence of folates 5-FU won't -- won't bind tightly to its target.

Q. Thank you, Doctor.

If could you turn to your declaration, Paragraph 176.

A. Sure.

Q. Your declaration, not your testimony.

A. Oh. I have to find that.

Q. Not your trial testimony. It's the thick document, probably towards the bottom.

A. It's on the bottom here somewhere.

Q. It's a thick one.

A. Got it. 176.

Q. 176.

A. Wait a minute. This has only got 133 pages in it.

Q. It's on Page 111. It's Paragraph 176 on Page 111.

A. Got it. Okay.

Q. You make a statement here. I just want to explore it a little bit.

A. Okay.

Q. You say, "The POSA, P-O-S-A, person of ordinary skill in the art, would recognize that mechanisms of folate transport were the subject of later, but pre-1999, work, (including work I personally -- I was personally involved in at the NCI), and to my knowledge there's no indication that such transport is B-12 dependent."

Do you see that?

A. Yes, I do.

Q. Okay. And so I guess what I'm getting at is, one of ordinary skill in the art in 1999 time frame, would one of the reasons they would give Tisman little, if any, weight is because it

was work done between 1985, when Tisman did his work on the folate pathway, up through 1999.

A. Yeah.

Q. Is that correct?

A. No. It really addresses a different point.

Q. Okay. What point are you addressing?

A. So he says in here, and the reason he's using B12 with -- with folate in this experiment with 5-FU is that B12 will enhance folate transport. It's in there.

Q. Mm-hmm.

A. And what I'm saying here is that subsequent work which purified the folate transporters. There were two transporters known at the time. One was the reduced folate transporter, which Ken Cowen cloned, and the folate binding protein or the folate receptor, which my group cloned. Neither group found any evidence that there was a B12 binding site on these proteins.

Q. Okay. So work subsequently --

A. So we didn't think it was transport.

What I -- my personal interpretation is these earlier experiments, that when you add B12

to a folate in a cell culture system you see an elevation of reduced folates which is due to the flux of 5-methyltetrahydrofolate through that pathway which it promotes.

Q. So if I understand you correctly, a person of ordinary skill in the art could read an article or reading an article could change over time based on work that was done since the time of the article?

A. Yeah. At the time this was done, it was a very limited understanding of transport. He claims it's -- that he added it to enhance transport. It probably didn't enhance transport. What it did is enhance the metabolism to a functional folate. But, you know, there's no way of my knowing that.

Q. Now, in the June 1999 time frame, looking at pemetrexed, would they -- would they consider pemetrexed reference -- prior art references to be more relevant than other references -- other antifolate references?

MR. GROSSMAN: Objection to the form of the question.

A. I'm not quite sure what you mean by that. Relevant to what?

BY MR. GABRIC:

Q. Well, let's look at the impact of folic acid pretreatment on toxicity of pemetrexed. All right?

Would one skilled in the art be more interested in references that discuss that concept, in the context of pemetrexed, than they would be with respect to references to discuss other antifolates and toxicity?

MR. GROSSMAN: Objection to the form of the question.

A. Well, my answer would be I think you would take the body of evidence about folates and antifolates into account. There's a lot of work done with methotrexate, obviously, because it was an approved drug and we were using it in patients. We had a very strong reason to try to understand that relationship between folates and methotrexate.

It would certainly be most pertinent to do the experiments with pemetrexed itself. But we're talking about actually having data. There's a lot of speculation in papers about what might happen or what might not happen. But actually having data, specific data to that point

would be very valuable.

Q. And in June of 1999 would one of ordinary skill in the art understand that methotrexate is not a TS inhibitor?

A. No. I actually did those experiments. Those are really important experiments.

Methotrexate is converted to a polyglutamate. In its primary form, the parent drug has a very low KM or KI for the -- for the enzyme. But as it's polyglutamated, it increases its affinity tenfold for every polyglutamate that is added. And it does eventually become an inhibitor of TS.

Now how important that is in terms of drug resistance, we don't know. Most of the drug resistance data indicates that its primary effect is on dihydrofolate reductase, but I think that question has never been settled. But there's no question that methotrexate is a TS inhibitor.

Q. Thank you.

All right. I think I'm done with 5-FU.

A. It's -- it's a difficult drug. It's an important drug, though. It's done a lot of good.

MR. GROSSMAN: Dr. Chabner, do you want to take a break or keep going?

THE WITNESS: Ten more minutes. Okay.

MR. GABRIC: Fair.

MR. GROSSMAN: If you're moving to another.

MR. GABRIC: This would be less than ten minutes. So we might as well knock one out of the way and we'll take a break.

THE WITNESS: Absolutely.

MR. GABRIC: The smaller this pile gets, the better off we are.

THE WITNESS: Yeah.

(Exhibit 1033 incorporated by reference.)

BY MR. GABRIC:

Q. I'm going to show you what's been marked as Exhibit 1033 in this proceeding.

For the record, this is European patent application 0595005. And you discuss this patent application in your declaration. Right?

A. Yes, sir.

Q. Okay. Do you know when is the first time you became aware of this document?

A. I imagine it was through my contacts with the legal team for Lilly.

Q. Okay. The legal team in connection

with this matter?

A. Yes.

Q. So it would have been within the last year?

A. Well, we've been working on this quite a while. No, it's not the last year.

Q. Yeah. To be fair with you, and if I get this wrong, I'm sure you'll correct me. I'm not so sure that the 005 application was at issue in the District Court litigation.

MR. GROSSMAN: It was an issue, as cited by Teva's counsel.

MR. GABRIC: It was.

BY MR. GABRIC:

Q. Okay. All right. So in connection with the District Court litigation you became aware of it?

A. Yeah. Right. So that's three or four years, actually.

Q. Three or four years ago or so?

Okay. Now, Exhibit 1033, what this reference does is it instructs one of ordinary skill in the art, as of June 1999, if you want to control your homocysteine levels, you can treat with a combination of B12 and folic acid.

Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Please restate it.

Q. Yeah. The Exhibit 1033, this EPO --

A. Yes.

Q. -- application, the title is "Pharmaceutical Preparations for Lowering Homocysteine Levels Containing Vitamin B6, folic acid and B12." Correct?

A. Right.

Q. And you've reviewed this reference. Right?

A. Right.

Q. And what this reference, at a high level, teaches of one of ordinary skill in the art, is if you're interested in controlling your homocysteine levels, you can do so by using a combination of Vitamin B12 and folic acid. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Well, I think that's simplifying it. It's -- it's saying that, you know, if you want to deal with the presumed toxicity of

homocysteine on the cardiovascular system, that's mentioned as the primary problem, myocardial and cerebral infarction, that you can use a combination of these vitamins to prevent that. And it really doesn't consider the special case of cancer, where these vitamins are required for cell proliferation. So it just considers this more general case. And in internal medicine, homocysteine levels are primarily the concern of -- of cardiovascular people.

Q. Can you turn to Page 11, Line 20, of Exhibit 1033.

A. Mm-hmm.

(Witness complies.)

Q. And at Line 20, what this document reference says is, "Furthermore, applicant has surprisingly found that for purposes of controlling blood homocysteine levels, the combination in accordance with the invention of PL, folate and Vitamin B12 reduces advantageous effects" and he goes on.

Do you see that?

A. I do.

Q. All right. So one of ordinary skill in the art in June of 1999, if they were interested

in controlling blood homocysteine levels, what this reference tells them that you can do that with a combination of Vitamin B12 and folic acid. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. It says that. That's -- that's true.

Q. And are you aware of any therapeutic benefit to elevated homocysteine levels?

A. Any therapeutic benefit?

Q. Benefit.

A. Why would you -- no, I'm not. I'm not sure anybody would consciously elevate homocysteine levels.

Oh, I can think of one instance, with methotrexate, you know, there's a therapeutic benefit to methotrexate, it has nothing to do with homocysteine.

Q. Right. But somebody is not going to go out of their way as far as you're aware of --

A. Infusing homocysteine?

Q. -- to raise their homocysteine levels?

A. Not really. No.

MR. GABRIC: This is a good time.

THE VIDEOGRAPHER: The time is 12:31.

We're off the record.

(Lunch recess was taken.)

THE VIDEOGRAPHER: The time is 1:25. We're back on the record.

BY MR. GABRIC:

Q. Welcome back, Doctor. I'm going to show you what's been marked as Exhibit 1032 in these proceedings.

(Sandoz Exhibit 1032 incorporated by reference.)

MR. GABRIC: For the record, this is the Carrasco paper or document, whatever you want to call it.

MR. GROSSMAN: Counsel.

A. It's a letter to the editor, actually.

Q. Okay. That's fine.

MR. GROSSMAN: I'm going to object to this as not being prior art.

MR. GABRIC: Noted.

Q. And you address this letter in your declaration. Correct?

A. I did.

Q. Okay. I just have a couple of questions about it. This is a -- I guess a letter that a doctor sent to -- about an

experience they had with a patient on methotrexate?

A. The -- yes. The patient is on a -- actually, on a multidrug regimen. Methotrexate, I think it was adriamycin. I can't remember what else. Being treated for leukemia.

Q. Right. And this physician treated this particular patient with a combination of folic acid and Vitamin B12. Correct?

A. Yes. The combination was treated for what they thought was acute megaloblastic anemia, which was something unrelated to the original disease, which was treated with methotrexate. So it was sort of like, well, look what happened to this patient. We should give him treatment for his megaloblastic anemia. It's a very strange case. Yes. And they did.

Q. So this patient was on a regimen of methotrexate, was suffering from some forms of toxicity and -- is that correct?

A. The treatment was given for megaloblastic anemia, which was not something that necessarily is related to methotrexate. I think it's just something that occurred as a second diagnosis.

Q. Okay. And so this patient had -- had this condition that you referred to while they were also being treated with methotrexate for cancer?

MR. GROSSMAN: Objection to the form of the question.

A. So that patient was treated with methotrexate and leucovorin rescue on day 14 after this treatment, they found a low platelet count and a high mean corpuscular volume and a low reticulocyte count and decided that he had a megaloblastic anemia and gave B12 and folic acid. I don't know if they gave him folic acid or not. I guess that was part of the regimen. Yeah. Folic acid.

Q. Yeah. If you go to --

A. Fourteen days. So this is sort of like something that happened after the treatment. He wasn't being treated to rescue the methotrexate.

Q. Okay. And I just want to get the sequence of events, as far as one of ordinary skill in the art would understand --

A. Yes.

Q. -- from this letter.

So this is a patient that was being treated

with methotrexate for their cancer, and at some point after the methotrexate treatment, some days after, they were then administered folic acid and B12 to deal with this other condition that was unrelated to the cancer?

A. That's right. That's right.

Q. All right. And did this physician anywhere in this letter express any concern that the administration of Vitamin B12 or folic acid, for that matter, would somehow undo the methotrexate treatment?

A. He didn't. I'm not sure why he did this, in the sense that his B12 level was normal. But that's what he chose to do.

(Sandoz Exhibit 1023 incorporated by reference.)

BY MR. GABRIC:

Q. Okay. I'm done with that, Doctor. Okay. I'm going to show you what has been marked as Exhibit 1023 in these proceedings. Once again, I'm not so sure how to pronounce the first name, the author's name.

A. Arsenyan.

Q. Arsenyan. Thank you. And you discuss this paper in your declaration as well. Correct?

A. Mm-hmm.

Q. And this is a mouse study that Arsenyan did?

A. It's a series of mouse tumors. Not all of it is a mouse study. No.

Q. Okay. Were the mice -- there was mice in the study that were injected with tumors. Right?

A. Right. But there was also cell line -- I thought there was some cell line work in here. No. I guess that's not right. They're all transplanted tumors.

Q. Sort of what Worzalla did. He transplanted tumors into his mice.

A. Yeah. Not the same tumors.

Q. And this paper was published in 1978. Correct?

A. Right. Well, it said 1978 it was submitted. I'm not sure when it was published. Oh, it's October of '78. Yeah.

Q. If you go to the bottom --

A. Right. It's October of '78.

Q. Is that '78 or 1979?

A. Right.

Q. So October '78 it was published?

A. Right.

Q. Okay. And the mice in this study were treated with methotrexate. Right?

A. Well, the first study is treating them with just methylcobalamin. That's Table 1.

Q. Right.

A. And then Table 2 takes it further, and he treats with combinations of methotrexate and cobalamin.

Q. The antifolate that is the subject of this paper is methotrexate?

A. Right.

Q. All right. And you've published extensively on methotrexate. Correct?

A. Yes.

Q. And you've never published -- none of your published papers reference this study of Exhibit 1023. Correct?

A. You know, I can't be sure about that because I published so many different things. For example, we did a whole series of reviews from 1980 to 1996 where we viewed a lot of other things. And I may not have referenced it in the book, but I was the editor. But I can't be sure that it wasn't in there. I -- I don't recall

using this as a -- as a reference, if that's what you're asking.

Q. And this work in Exhibit 1023, this was the result of a collaboration with some Russian researchers. Is that correct?

A. It wasn't a collaboration with me personally. It was with the National Cancer Institute. The developmental therapeutics program in which we provided some reagents for them.

Q. And "we" being the National Cancer Institute?

A. Yes.

Q. Were you personally involved at all in this collaboration?

A. I was the director of the division of cancer treatment; not at this time, although I was involved in the Russian collaboration at this time as a representative of NCI. I went to Russia in 1976, actually, the first time, and met a number of their researchers. I don't remember ever meeting this guy or any of the people on the paper.

Q. And did this collaboration, did it involve other work aside from the work --

A. Yes.

Q. -- that's reported here?

A. Yes.

Q. Okay. So were you aware of the work that's reported in Exhibit 1023, contemporaneous with the time it was taking place?

A. You know, I was aware of aspects of it. For example, one of our people who was very instrumental in the collaboration was a guy named Abe Golding, who had done a lot of work on methotrexate, and I have a feeling he must have been involved with this as an instigator of some of this work. There's a subsequent paper which was done that cited Sofyina where, again, there were compounds provided by the NCI.

Q. Now, as we discussed, the antifolate that was the subject of this paper is methotrexate. Right?

A. Yes.

Q. Okay. And in Table 2, it refers to pretreating with methylcobalamin.

A. B12.

Q. B12?

A. Yes.

Q. Well, is -- is -- isn't B12 cobalamin?

A. Well, the form that's given, B12 for people, is cyanocobalamin. It's converted metabolically to methylcobalamin. So you could use methylcobalamin instead, but it's all B12.

Q. But it's methylcobalamin, not cyanocobalamin?

A. Right.

Q. And for a person of ordinary skill in the art to conclude that the results would be the same with -- as reported in this paper with cyanocobalamin, they'd actually have to run the tests with cyanocobalamin. Right?

A. Right. Although you never can be quite sure. I'm not sure what the source of all the cobalamins were here. So you're right, you'd have to do the experiment. It would likely turn out the same, but I'm not sure.

Q. And with the mice -- I'm looking at Table 2 -- that were pretreated with the methylcobalamin, they had an increase in lifetime by a couple of days. Is that correct?

A. Wait a minute. You better repeat that question.

Q. Yeah. I'm looking at Table 2.

A. Yes. Which line?

Q. The -- I'm looking at increase in lifetime of animals --

A. Yes.

Q. -- percent.

A. And which -- which --

Q. I mis- --

A. Which -- which line?

Q. Yeah. Let's look at -- I misread it. So I'm glad you asked.

A. Yeah. Go ahead.

Q. Yeah. It reports here that for the mice on the methylcobalamin pretreatment with methotrexate experienced a 21 percent increase in lifetime versus those that weren't pretreated.

A. Let me see. Yeah. It's -- it's -- it's 21 percent increase in lifespan compared to those treated with methotrexate alone, I believe.

Q. And one of ordinary skill in the art in June of 1999, looking at this document, would understand that. Correct?

A. Well, what they would understand is it's not a statistically significant difference.

Q. And they would -- whether statistical or not, they would understand that this reports a 21 percent increase in lifetime?

A. Usually we want statistics in our experiments. So it -- the other thing that's notable about that is that it's -- it prevented the inhibition of growth of the tumor by methotrexate. If you compare that last line to the first line, methotrexate inhibited on the first and second day, 94 percent, and the combination of pretreatment with methylcobalamin plus methotrexate led to an increase in size of 36 percent. So there's a marked difference.

Apparently by the time the animals died, there was no significant difference in their -- in the outcome. That's hard to explain. I really am puzzled by that, because if you get a stimulation of growth in the first seven or eight days, why wasn't there an increase in lifespan? But it is a nonstatistically significant difference. So maybe -- who knows. I don't know what they showed. They don't give other data to help you.

Q. But the authors went to the trouble in Table 2 to report this 21 percent increase in lifespan. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. They did go to the trouble. Yes.

Q. Okay.

(Discussion off the record.)

Q. So, now, for the mice that were just on methylcobalamin, there was no increase in lifespan whatsoever, or 0 percent. Right?

A. Pardon? I was looking at --

Q. I'm in Table 2.

A. Okay. So what were you saying?

Q. So the mice that were treated with methylcobalamin alone, they experienced no increase in lifespan. 0 percent?

A. Right.

Q. And the mice that were treated -- pretreated with methylcobalamin followed by methotrexate, they experienced a 21 percent increase in lifespan. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Right.

Q. So there is a statistical difference between the --

A. Which one?

Q. -- methylcobalamin-alone mice and the mice that --

A. I don't think you can draw that conclusion.

Q. You don't -- 0 percent increase in lifetime versus 21 percent?

A. No. But, look, look at the p-values here. Do you know what a p-value means? I shouldn't be asking you questions. But that is a measure of statistical significance. And there's no -- oh, wait a minute. No, but it's -- the comparison is relative to methotrexate alone. It's not to cobalamin.

Q. Right. Okay.

A. So there is no -- there is no comparison there.

Q. I'm going to show you what we've -- what's been marked as Lilly Exhibit 2041.

(Lilly Exhibit 2041 incorporated by reference.)

A. Sure.

Q. And I believe this is the Sophyna -- have I got that right? Sophyna paper.

A. You got it.

Q. All right. And you discuss this paper in your declaration, correct?

A. Yes.

Q. And if you go to Page 16.

A. Sixteen?

Q. Yeah. The lower right-hand corner, it's Lilly Exhibit 2041. Page 16. Just for the record, what I believe this exhibit purports to be is a Russian language version of the paper with an English language translation that Lilly had done.

A. That's right.

Q. But the Russian's version, the Russian language version did contain an English language abstract. Correct?

A. Right.

Q. And that's on Page 16 of this exhibit. Correct?

A. That's right.

Q. And if I understand your opinion correctly, where it says, "the effect of methylcobalamin" in the summary --

A. Yes.

Q. -- the reference to methylcobalamin, that's a typographical error?

A. Yes.

MR. GROSSMAN: Objection.

A. It should be methylcobalamin analogs,

which showed synergy with methotrexate. When you use methylcobalamin alone, it's caused tumor stimulation, and I couldn't find anywhere in the paper where it said methotrexate with methylcobalamin caused enhancement. I could find plenty of areas where it showed enhancement with methylcobalamin analogs.

Q. So we're referring to the last sentence of the abstract --

A. Yes.

Q. -- which says, "The most effective inhibition of tumor growth in the longer survival of the animals were achieved in combined application of methylcobalamin with methotrexate" --

A. Right.

Q. -- etc.

A. Right.

Q. You think one of ordinary skill in the art would understand --

A. It should be cobalamin analogs.

Q. So one of skill in the art would understand it to be a typographical error?

A. Well, I would hope so, if they look at data.

Q. And that's a fairly material typographical error --

A. It is.

Q. -- right?

A. Well, Russians aren't perfect --

Q. Okay. Would one of skill --

A. -- despite what Donald Trump says.

No. We looked at this carefully, because it seems to me, you know, totally inconsistent with what's in the paper. And if you look in the paper, the various experiments that were done, there's nothing here that I could find that shows methotrexate with methylcobalamin causing enhanced activity, antitumor activity. It's all with these various analogs, which are inhibitory.

Q. If one of ordinary skill in the art was made aware -- let's assume an English-speaking one of ordinary skill in the art -- that this was a typographical error, would that cause them to question the accuracy of the other data in this paper?

A. Well, it might, you know, but I think that they do give the data. So, you know, it might. But whoever translated, you know, I don't know who that was. It could have been -- it

could have been that one point of inaccuracy. But the data actually is pretty consistent in the paper. And I think that's what is important.

Q. And if we assume this is a typographical error and it's referring to -- I'm sorry. Strike that.

A. The analogs.

Q. Strike that. And I believe Sophyna is also -- the antifolate that's the subject of this paper is methotrexate?

A. That's true. Actually, if you look at the paper itself, there is a nice paragraph which says, "The increase in tumor growth retardation in the animals' lifespan was noted with a combined exposure to methylcobalamin, chloroplatinate," which is an analog, "and the quinone derivatives, the NCI drug. Given the amplified action methotrexate when used in combination with these analogs and methionine and synthase inhibitor, we performed combination experiments in mice with -- using all three inhibitors." And that's shown in Table 3. I guess it shows the same thing there.

Q. And cyanocobalamin is not the topic of this paper?

MR. GROSSMAN: Objection to form of the question.

A. Well, yeah. No. It's one of the active B12 forms. There are multiple active B12 forms. Yes. I doubt if the result would have been any different with the other form. But you never can be sure. I mean, you know, I don't -- I'm not absolutely sure.

Q. I show you what's been marked as Exhibit 1017 in the Neptune proceedings.

MR. GABRIC: Oh, I'm sorry. I've got to mark that.

MR. PERLMAN: Wait. Before you do that, you have to give it a number for your proceeding or --

MR. GABRIC: Yeah. That's what we're going to do. May I have that back real quickly, Doctor?

THE WITNESS: Sure.

MR. GABRIC: I've got to dot my Is and cross my Ts.

MR. PERLMAN: It's a massive disaster over there.

MR. GABRIC: Thank you. I'm going to mark as Exhibit 1069, which is a paper by Allen.

Ask if you've seen that document before.

(Article entitled "Diagnosis of Cobalamin Deficiency I: Usefulness of Serum Methymalonic Acid and Total Homocysteine Concentrations" marked Exhibit 1069.)

A. I guess I have. You know, I certainly know the document. I don't know what -- I can't remember exactly in what context, what part of this trial. But I have seen it. I know the people that did it.

Q. And if you go to Page 93 --

A. Got it.

Q. -- the first full sentence, it says, "Approximately 95 percent of these Cbl deficient" -- I think that's B12 deficient?

A. Mm-hmm.

Q. -- "had elevations of serum MMA, methylmalonic acid."

A. Yes.

Q. Okay. And so one of ordinary skill in the art in June of 1999 reading this paper would understand that approximately 5 percent of those Vitamin 12 deficient would not have elevated MMA levels?

A. We don't -- we know that they have low cobalamin levels. There's a difference between having low levels and being functionally deficient. You actually brought that point out with the folates and that we were talking about functional folate deficiency.

What homocysteine measures is functional deficiency rather than the serum level. And so people concerned with this kind of research, in general, have relied on homocysteine to confirm that there's a functional deficiency.

Q. So I just want to make sure I understand something. The -- one of ordinary skill in the art in June of 1999, their takeaway from the Allen paper is that approximately 5 percent of those individuals who are Vitamin B12 deficient --

A. Are low levels.

Q. -- low levels of B12 do not have elevated MMA levels?

A. Right.

(Lilly Exhibit 2058 incorporated by reference.)

BY MR. GABRIC:

Q. And I'm going to show you what -- I'm

going to show you Lilly 2058. This is the McLean paper that you referred to in your declaration. Do you recognize this?

A. I do.

Q. And McLean reports on some experiments with cancer cell lines.

A. That's right.

Q. And McLean does not report any tests on live animals or people. Correct?

A. No.

Q. Yes, I'm correct?

A. Yes. You're --

Q. And the -- the study reported in McLean did not involve administrating any antifolate or any anticancer agent. Correct?

A. Well, I think the intent was that these drugs would become anticancer agents.

Q. But he does not report doing tests where he was actually administrating any anticancer agents or antifolates to animals or human beings?

A. Well, there are cell lines experiments with analogs to see if any of them inhibited cell growth. So -- and these are cancer cell lines, so this is an anticancer experiment.

Q. Right. But it's not in a live animal or human being. Correct?

A. No. No, it isn't.

Q. Now, in the abstract, the end, McLean reports, "These results indicate that modifications of the" -- I think that's "E-position of Cbl...", which is Vitamin 12, "...abolish the ability of Cbl to support cell growth and generate potent inhibitors of Cbl-dependent cell growth."

Do you see that?

A. I remember, but I can't exactly find it. Oh, yeah. Right. I found it.

Q. So this paper reports to one of ordinary skill in the art in June of 1999 that changes to cobalamin compound can have a material effect on the anticancer effect. Correct?

A. Yeah. Right. But these are -- let me be -- clarify that. This is not difference between cyanocobalamin and methylcobalamin, if that's what your point is. This is a -- these are structural changes in different parts of the molecule.

Q. And those structural changes had a material impact on the effect of that molecule?

A. On certain parts of the molecule only. Some were -- were potent. Others weren't.

Q. Have you -- you used the term "methyl trap" in your declaration?

A. Yes.

Q. Have you ever published any papers on the methyl trap?

A. You know, it would be hard for me to say. I'd have to look through a lot of papers to tell. I've published a book in which we discuss it. Yes.

Q. Have you -- as you sit here today, can you identify for me any of your publications --

A. My personal publications?

Q. Yes.

-- where the focus was on the methyl trap?

A. I have to think about that. Probably not. Not peer-reviewed papers. I published books about -- in which this was discussed. Yes. But I was editor of Goodman and Gilman's, which has a large section on this.

Q. So somebody else wrote it and you were the editor?

A. I rewrote it.

Q. For stylistic changes?

A. No. For substance as well. No. I was very involved in that.

Q. So can you, as you sit here today, identify any papers that you rewrote that were specific to the methyl trap?

A. Probably parts of it. You know, it's hard for me to -- I was a very active editor of this. I was one of three editors of the standard Textbook of Pharmacology. And this was part of my assignment.

Q. Now --

A. I guess the point is that I do feel I understand this. You know, this is part of my field of expertise.

Q. I'm going to show you what's -- I show you Lilly Exhibit 2037.

(Lilly Exhibit 2037 incorporated by reference.)

BY MR. GABRIC:

Q. And this is a paper you referred to in your declaration. And for the record, it's the Dierkes or Dierkes?

A. Dierkes.

Q. Dierkes paper. So this is a study that Mr. or Dr. Dierkes is reporting regarding

supplementation with B12 to decrease homocysteine and MMA levels?

A. Yes.

Q. And if you look at 634, it looks like there was, what, 14 patients that were the subject of this study?

A. Thirty-four.

Q. Up in the left-hand corner. After supplementation, 13 of 14 patients had serum folate concentrations below the reference limits.

A. Yes.

Q. So this was a 14-patient study. Right?

A. Okay.

Q. It's a 14-patient study. Correct?

A. Right. Well, I'm not sure that those are all the patients they studied. They said after supplementation, 13 of 14 had serum folate levels below the reference limit. So of the group they studied, this subset had it. I think --

Q. If you look at the abstract --

A. I'd have to look at the abstract to see how many patients they studied, in general.

Q. Yeah. On the fourth line it says N=14. I don't know if that helps you.

A. Eighty-five patients, they studied.

Q. Where are you picking up the 85 patients?

A. Page 631.

Q. Where on 631, Doctor?

A. On the right-hand side, under "Subjects and Methods."

Q. Okay. Gotcha. Okay. And of those 85, 14 had low serum cobalamin levels?

A. Right. They're basically studying a group of patients who are on hemodialysis, which really affects a lot of different things in the blood, you know. Do you know what dialysis is?

Q. Yes, sir.

A. Yeah.

Q. And on Page 633, if you look at the -- right above Figure 2, it says, "although the number of patients is too small to make firm conclusions." Do you see that?

A. Where is this? I don't see it, no.

Q. Above Figure 2, there's text.

A. Oh, yes. About the T allele.

Q. So Dierkes is conveying to one skilled in the art that this study is not sufficiently large to draw any firm conclusions?

A. Right.

MR. GROSSMAN: Objection to the form of the question.

A. I don't know what you're talking about there, actually. It has to do with the T allele of methyltetrahydrofolate reductase.

Q. And anywhere in this article by Dierkes, does he refer to -- does he use the phrase "methyl trap"?

A. You know, I'd have to read it carefully to know. I don't know. Why?

Q. If you can't point to it right now --

A. I don't.

(Discussion off the record.)

Q. Now, in your declaration, you've offered some opinions about one of ordinary skill in the art would look at alternatives other than pretreating with folic acid and Vitamin B12 to address toxicity. Correct?

A. That's right.

Q. You talk about adjusting the dose and frequency of pemetrexed.

A. (Witness nodded.)

Q. And you talk about using rescue therapy?

A. (Witness nodded.)

Q. Or perhaps lowering homocysteine levels with betaine or --

A. Betaine.

Q. Betaine. And as of June of 1999, one of ordinary skill in the art would have understood that pretreating patients with folic acid could reduce pemetrexed's toxicity. Correct?

A. Might. I would say might. Yes.

Q. And, in your view, one of ordinary skill in the art would have considered pursuing dosing or scheduling adjustments as an alternative to pretreating with folic acid. Correct?

A. Yes.

Q. That dosing and scheduling adjustment would be a better alternative than pretreating with folic acid?

A. Well, you're faced with a situation in which you have a subset of patients who have high homocysteine, just a subset. It's not all the patients. A small number of them. So why give these vitamins to all patients and risk tumor progression when you can identify that subgroup

and you could do things with that subgroup, such as dose adjustments or rescue that are conventional approaches to dealing with toxicity, without risking the issue of giving the vitamins?

Q. So dose adjustment or rescue would be a preferred alternative to pretreating with folic acid. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Right. It's a well-accepted and established way of dealing with toxicity. Yes.

Q. And so a person of ordinary skill in the art would have these alternatives available to them. Right?

A. That's right.

Q. Adjust dosage or treatment schedule. Correct?

A. Yes.

Q. Or rescue therapy?

A. Yes.

Q. Or pretreat with folic acid?

A. Well --

MR. GROSSMAN: Object.

A. -- I wouldn't have accepted pretreatment of folic acid as -- in the same

category as the others, because the others are well-established approaches in the treatment. Pretreatment with a vitamin that you know stimulates tumor progression -- and there's evidence of that, we've covered it -- doesn't make that much sense to me.

Q. It would be less preferred to a person of ordinary skill in the art?

A. I would not do it. I wouldn't have done it. I never have done it until pemetrexed was shown to be effective in 2003 and came available.

Q. So in June of 1999, a person of ordinary skill in the art would have preferred to pursue dose adjustment, scheduling changes or rescue therapy as opposed to pretreatment with folic acid?

MR. GROSSMAN: Objection to the form of the question.

A. I'd say more than preferred. I just wouldn't have done it.

Q. Now, in June of 1999 time frame, a person of ordinary skill in the art, when administrating chemotherapy, they'd be basically looking at two things. Right? Efficacy and --

and minimizing or, if you can, avoiding toxicity. Right?

A. Yeah. Well, the major objective of treating cancer patients is to try to get rid of the tumor. And you want to do it in a way that's safe for the patient.

Q. Right. And in June of 1999, a person of ordinary skill would understand that you want to administer chemotherapy in an amount of the drug that you would achieve the desired efficacious effect and would also not cause unacceptable toxicity?

A. Right.

Q. And one of ordinary skill in the art in June of 1999 would have understood that that would be an objective with pemetrexed. Correct?

A. That's right.

Q. And so one of ordinary skill in the art, in June of 1999, if they could reduce toxicity of chemotherapy agents, such as pemetrexed, by pretreating with a vitamin, and that pretreatment resulted in a decrease in efficacy of the agent, but the efficacy was still acceptable to reduce tumor growth, they would pursue that course of treatment. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. We already had a trial that showed it didn't work. The Hammond trials. We went through that this morning. And it was -- it didn't provide any encouragement for pursuing that. Secondly, the literature at that time told us that the current regimen with pemetrexed was manageable, the toxicity was manageable and easily dealt with by the usual things of dose adjustment and -- I mean, the papers are here.

Q. Yeah. The papers say what they say. Let me ask you a hypothetical. Okay? This is a hypothetical question. I'm one of ordinary skill in the art in June 1999. And I can pretreat my patients with vitamins such as B12 and folic acid. I know I can do that and reduce toxicity. And whatever efficacy impact it may have, the efficacy is still sufficient to treat the tumor. Wouldn't I pursue that course of action?

A. Well, that wasn't known to a person of ordinary skill --

Q. This is a hypothetical.

A. Yeah. But it wasn't known. I mean, if you told me the same thing about any other drug,

if I could give vitamins to people taking adriamycin, and it wouldn't make any effect, I would say, yeah, but, you know, it's not -- I think it's an extremely unlikely hypothetical. And it's unnecessary, because you have a regimen that works that has manageable toxicity.

Q. And -- but for purposes of my hypothetical, if you accept one of ordinary skill in the art would understand that I can -- I can moderate my toxicity with pretreatment with Vitamin B12 and folic acid, yet still have sufficient efficacy to treat that cancer, I as one of skill in the art would pursue that approach?

MR. GROSSMAN: Objection.

A. I would say show me the data. If you had data that showed that, I would look at it. I would -- I would be interested. But as of June of 1999, that kind of data was not in the public domain.

Q. And if this hypothetical -- under this hypothetical this data was in the public domain, then that data would suggest to the person of ordinary skill in the art to pursue that route; namely, pretreat with folic acid and B12?

A. Well, if I had a reason to do that, then I would have. But the regimen was manageable and the toxicity wasn't excessive. And our references say that repeatedly. It's manageable with dose adjustments and -- and attention to renal function.

There is that subset with the homocysteine elevation which could be singled out for particular regimens. But that would certainly not prompt me to treat everybody with the vitamins. But I wouldn't treat those people with the vitamins. I would just use dose adjustment and rescue, which was -- were accepted ways of doing the toxicity.

I certainly would be very cautious about using the vitamins which could stimulate tumor growth and negate antitumor activity. And there was plenty of evidence that that was the case in the prior literature. So that's my opinion. Okay.

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

THE VIDEOGRAPHER: The time is 2:15. We're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: Here begins Disk 5 in the deposition of Bruce Chabner, M.D. The time is 2:29, and we're on the record.

BY MR. GABRIC:

Q. Doctor, I show you what's been marked as Exhibit 1045 in these proceedings.

(Sandoz Exhibit 1045 incorporated by reference.)

BY MR. GABRIC:

Q. It's sometimes referred to as Calvert II. You refer to this document in your declaration. Correct?

A. Yes.

Q. And Calvert reports -- I'm on Page 106 -- in the right-hand column, the bottom third, there's a sentence that says, "however, such toxicities." Do you see that?

A. Yes.

Q. Okay. It says, "Calvert reports, however, such toxicities have not been a serious problem in those Phase 2 studies in which patients were, in general, of a good performance and nutritional status."

Do you see that?

A. Yes.

Q. And this is a discussion of Phase 2 studies of pemetrexed?

MR. GROSSMAN: Objection to the form.

A. Yes. I guess that's right. I'm not sure what he means by "general" -- "in general, a good performance status and nutritional status." I'm not sure that -- yeah. Okay.

Q. So what Calvert is explaining here to one of ordinary skill in the art in June of 1999 is there's a connection between nutritional status and homocysteine levels. Correct?

MR. GROSSMAN: Objection to form.

A. As I said, I'm not sure exactly what he means by that, but I'll take it at face value.

Q. Well, he goes on to say, "The recently presented study of the use of plasma homocysteine as a marker for folate deficiency shows a correlation between elevated pretreatment homocysteine levels and the subsequent occurrence of Grade III or IV toxicity."

Do you see that?

A. Yes, I do.

Q. So what Calvert is reporting to one of skill in the art here as of 1999 is that he's talking about looking at the nutritional status

and the homocysteine levels when you figure out whether you'll be able to administer pemetrexed safely every three weeks. Right?

MR. GROSSMAN: Objection to the form.

A. Yeah, you know, I think that was his conclusion, that you could.

Q. And Footnote 14, that's a cite to the Niyikiza abstract --

A. Right.

Q. -- that we discussed earlier.

Now, Calvert is talking about Grade III or IV toxicity. What is a Grade III and Grade IV toxicity?

A. Grade III -- the toxicity is graded according to severity. Minor toxicity is a Grade I and perhaps Grade II. Grade III in a nonhematologic toxicity is considered a serious toxicity, too. And there are various ways of describing those toxicities. A scheme for -- for grading toxicities for liver or for other -- other tissues, skin.

And Grade III-- III hematologic toxicity is a modest but significant depression of white count or platelet count. And Grade IV toxicity is a dangerous decrease in counts if it's -- if

it's maintained a significant period of time.

So you would hope that the drug would produce a limited number of Grade III and Grade IV toxicities, particularly Grade IV toxicities to the bone marrow.

Q. And when Calvert is referring to toxicities not being a serious problem, would one of ordinary skill in the art have an understanding of what grade of toxicities he's referring to here in this passage?

A. It -- basically one would understand it that the schedule that has been developed is safe and effective -- well, safe, at least, and the efficacy is a separate question. But safe, and it -- the toxicities are manageable.

So with all cancer drugs of this kind, chemotherapies, there are toxicities which we expect and learn how to manage. It doesn't mean that they don't exist, they don't happen. But by this point, 1999, a person of ordinary skill would know that chemotherapy produces toxicities and there are ways of managing it. So...

Q. In June of 1999, would one of ordinary skill in the art consider a Grade IV toxicity safe and manageable?

A. Yeah. You wouldn't want a 30 percent incidence, but, you know, a 5 percent incidence, yeah. Sure.

Q. Well, the 5 percent of people who had the Grade IV toxicity --

A. It's not 5 percent of people. It's 5 percent of cycles of treatment.

Q. I see.

A. A good example is in some of the lung cancer studies that we've looked at, there are five cycles -- four or five cycles of Grade IV toxicity out of 120 cycles administered. So that means, like, you know, 5 percent or less of patients have that kind of toxicity. And it was well managed.

Q. I show you what's previously been marked as Exhibit 1047 in this matter.

(Sandoz Exhibit 1047 incorporated by reference.)

Q. And this is, I think, sometimes referred to as Calvert III. And you refer to it in your declaration. Are you familiar with this document?

A. Yes.

Q. Now, on Page 39 under "The Future for

MTA," do you see that?

A. Page 39. Yes, I do.

Q. MTA is pemetrexed?

A. Yeah.

Q. It says, about six lines down, "The dose-limiting toxicities were usually hematological." Do you see that?

A. Yes.

Q. What would one of ordinary skill in the art in June of 1999 understand dose-limiting toxicity to be referring to?

A. That the toxicities that occurred that limited the amount of drug you could give were bone marrow-related toxicities.

Q. And so Calvert is reporting here to one skilled in the art that there are dose-limiting toxicities associated with pemetrexed. Correct?

A. Yes. I mean, in some patients, a small percentage of the patients.

Q. And further down, when he's talking about the future of pemetrexed, it's the fourth paragraph, the second to last paragraph on the acknowledgments, he says, "trials are planned."

Do you see this?

A. Yes.

Q. "Trials are planned to investigate the effect of folates on the toxicities seen with MTA, based on the observation that animals given folate supplements were better able to tolerate treatment with MTA with fewer side effects."

Do you see that?

A. I see that.

Q. And he cites to Worzalla.

A. Right.

Q. And that's the Worzalla abstract we talked about earlier today. Correct?

A. Right.

Q. And that's the mouse study from Worzalla?

A. Right. That's not a human study. There was a human study.

Q. And based on the observation in animals, they're not going to move on to humans.

A. Yeah. They did. They did move on to humans.

Actually, you know, related to your question, on Table 2, it gives the incidence of toxicities in the various schedules. And it shows neutropenia three or four -- four in these patients on the weekly schedule, and I believe

that was 600, which was a higher dose.

But, you know, it's a relatively small incidence, considering that each patient received three or four cycles of treatment. So four of the cycles had Grade III and five had Grade IV. And it gives the same data for the other schedules tried in Phase 1, and the other two schedules were about the same toxicity level, except that they didn't produce as many clinical responses. So they decided to go with the three weekly schedules.

Q. So Calvert III here -- and you rely on Calvert III for the teaching that toxicities were tolerable and manageable?

A. Right.

Q. Yet, even though Calvert reported that to one of ordinary skill in the art, he's also telling one of skill in the art that, nonetheless, we're going to move forward and investigate folic acid pretreatment with pemetrexed in human beings?

A. Yes. And the reason was that they were hoping that they would have greater antitumor efficacy by doing that. They would be able to increase the dose and get more tumor responses.

Q. And increase the dose, while minimizing the toxicity?

A. Well, they would probably drive it to the same level of toxicity, but trying to increase the dose to get more efficacy. That's, in general, the motivation.

Q. Right. And one of ordinary skill in the art in June 1999 would have understood when you increase the dose of pemetrexed to get more efficacy, you now run the risk of getting more toxicity?

A. That's right.

Q. And so folic acid was a potential solution for that toxicity.

A. Well, it's not the total solution, because they ran into renal problems.

Q. In June of 1999, Calvert is pointing to folic acid.

A. This is 1998 --

Q. Okay.

A. -- and it's probably written in 1997. So it's -- you know, it's -- there was more known in 1999. We had the Hammond studies in people, the very experiment that he said that he was noticing was going to be done. And it was done.

Q. And so just so I'm clear, one of ordinary skill in the art would have understood in June 1999, even though Calvert had mentioned here the toxicities are tolerable and manageable, he's reporting that we're going to investigate folic acid pretreatment with pemetrexed?

MR. GROSSMAN: Objection to the form of the question.

A. I think you've ignored what I said. And that was that they did try it, and it didn't work.

Q. Well, we got at least one partial response. They were aware of it. Right?

A. We've talked about that.

Q. And there was a reduction in toxicity. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Not really. New toxicities. New problems.

Q. All right. Let's -- let me show you what's been marked as Exhibit 1052.

(Sandoz Exhibit 1052 incorporated by reference.)

BY MR. GABRIC:

Q. Now, this is the Rusthoven?

A. Rusthoven.

Q. Rusthoven.

A. Rusthoven.

Q. We'll go with Rusthoven reference. This is discussed in your declaration as well. Right?

A. Right.

Q. Now, if we go to Page 1198. And just big picture, this is reporting some Phase 2 study work on pemetrexed?

A. That's right.

Q. Now, Page 1198, on the left-hand side, the last full paragraph, Rusthoven reports that there was a decision to reduce the starting dose from 600 to 500 milligrams early in the study. Do you see that?

A. Yes, I did.

Q. And that decision was based largely on toxicity.

A. Right.

Q. So one of ordinary skill in the art reading this would understand that this Phase 2 study, because of toxicity issues, the starting dose was reduced from 600 to 500 milligrams?

A. Right.

Q. And then if you look at Page 1196, some of the patients that were started at 500 milligrams had to be reduced further because of toxicity issues. Right?

A. Right.

Q. And of 30 patients who started at 500 milligrams, 15 received one cycle at that dose. The other 15 did not receive a second cycle at that dose. Correct?

A. Wait a minute. Where are you -- I was looking at something else. Where are you?

Q. I'm sorry. 1196, under the results. It says --

A. Right.

Q. -- about ten lines down or so, "Of the 30 patients who started at the 500-milligram dose, 15 received one cycle at this dose."

A. Right. And 15 had a dose reduction.

Q. The other 15 had a further dose reduction?

A. Right. Well, it says five received one cycle. Four received two. And 11 received three or more. So a number of them continued at that dose. Fifteen of them didn't continue at that

dose. Some of them were dropped for other reasons. One had a stroke. One had a cerebral hemorrhage or cerebral event, I don't know. Pulmonary embolus, I guess it was. And a few only received one cycle and then were further dose reduced.

Q. So of the 13 patients that started at 500, 14 patients required a dose reduction to 375. Right?

A. Right.

Q. And then four of those received a further dose reduction to 281. Correct?

A. Right.

Q. So toxicity was causing dose reductions --

A. Yeah.

Q. -- in this Clinical 2 trial?

A. Well, they were having a particular problem here with a rash. Do you see on Page 1198? This is a drug that caused -- if you don't pretreat with steroids, you get a rash. It was very symptomatic. And so it says 30 percent of patients had treatment delayed with no subsequent dose reduction, whereas patients with generalized symptomatic rash, 39 percent were

given a 25 percent dose reduction.

And that, they found out subsequently, was very easily managed by just giving dexamethasone for three days before starting each dose. So I think we found subsequently that the 500-milligram dose is well tolerated. Of course, we're using a different schedule, but we're not seeing the rash. And I think that they would have fewer dose reductions, significantly fewer if they had not had this cutaneous toxicity.

Q. So one of ordinary skill in the art would understand in June 1999 that these dose reductions --

A. Uh-huh.

Q. -- could have an impact on the efficacy of pemetrexed on the cancer?

A. Right. It could have. As I said, I think they very quickly devised a way of avoiding many of these dose reductions by -- by using dexamethasone. And that's still being done today.

(Discussion off the record.)

BY MR. GABRIC:

Q. Now, on Page 1195, under "Drug Administration" --

A. Yes.

Q. -- it says, "Support of cure agents such as colony stimulating factors were permitted" --

A. Yes.

Q. -- "but could not be substituted for dose reductions required according to the protocol." Do you see that?

A. Yes.

Q. Okay. So would one of ordinary skill in the art understand that this is a reference to granulocyte?

A. Granulocyte stimulating factor.

Q. Yeah.

A. Yeah.

Q. And so these patients were provided --

A. I'm not sure everyone was. What does it say? Some patients. I just can't find it. I'm sorry.

Oh, okay. Yeah. Colony stimulating factors were permitted, but could not be substituted for dose reductions required. So the idea is this, that if they gave the drug and the white count dropped below a certain level, they would reduce the next dose, no matter whether they were able

to give that patient G-CSF and the counts just bounced right back up and nothing happened.

Subsequently, in the last, I'd say, 15 years, G-CSF is routinely used in patients, and you just continue at the same dose, if you have to. You'd be less likely to reduce the dose. It depends on a lot of other issues, though.

Q. And so in the "Results" section on the first page of the paper --

A. Yes.

Q. -- he reports that in this Phase 2 study with pemetrexed, 39 percent of the participants experienced Grade III or IV -- what is that?

A. I'm not following you. I'm sorry.

Q. I'm sorry. I'm on the very first page.

A. What is the page number?

Q. Oh, I'm sorry. 1194.

A. Oh. Okay.

Q. He reports -- and I'm on the right-hand side.

A. In the summary.

Q. In the summary. Four patients, 123.3 percent experienced febrile neutropenia --

A. Febrile neutropenia.

Q. -- febrile neutropenia and 13, 39 percent, experienced Grade III or IV neutropenia.

A. Neutropenia. Mm-hmm.

Q. So one of ordinary skill in the art reviewing Calvert would understand that 39 percent of the participants in this study experienced a Grade III or Grade IV neutropenia toxicity?

A. Right. At some point.

MR. GROSSMAN: Objection to the form of the question.

A. Yeah. You have to realize, though, that when you're talking about patients, each patient had multiple cycles of treatment. So it could have been after the seventh cycle, right. So six cycles without and the seventh cycle, they got it.

But, in general, I think the number of cycles given here was 120 cycles. So if it's -- you know, it's one event, 13 events out of 120 cycles, that's about 10 percent of the cycles. And most of those were manageable.

And we often see with cancer chemotherapy agents suppression of the white count. But if --

the key thing is if it bounces back quickly, patients don't get into trouble.

Q. Okay. Well, let's go to Page 1198.

(Witness complies.)

Q. Go about 14, 15 lines down. Calvert reports that 30 percent of patients came off protocol therapy because of toxicity, most often gastrointestinal. Do you see that?

A. Yeah. I do -- No. It's not all gastrointestinal.

Q. Most often gastrointestinal?

A. Well, if you really look at the toxicities here, two of the patients came off for other events that were unrelated to the drug. And one of them was a patient at 600. And they dose reduced because of the toxicity they saw at 600.

So you're left with seven patients out of 30 that discontinued the drug for various reasons. And the reason -- and part of the reason was the rash, which they learned to manage. And I don't think that's an unusual rate.

Q. Just so I'm clear, the Calvert reports, 30 percent came off the therapy because of toxicity?

MR. GROSSMAN: Sorry. I just -- you've done this a couple of times. Just for clarity, it's not Calvert.

Q. Calvert. I'm sorry. I'm sorry. Rusthoven. Thank you.

A. Yeah. Well, I explained that. You have my answer.

Q. And some of the patients in this study may have gotten the G-CSF?

A. Yeah. That would be after they got the neutropenia.

Q. Go to --

MR. GABRIC: I show you what's been marked as Lilly Exhibit 2029.

(Lilly Exhibit 2029 incorporated by reference.)

BY MR. GABRIC:

Q. This is the O'Dwyer paper. And you refer to this in your declaration?

A. This is Bertino. Oh, you mean the O'Dwyer paper in the Bertino volume.

Q. Yes. Correct.

A. I see.

Q. And this paper reports on Phase 2 trials of pemetrexed?

A. Right.

Q. Now, he discusses in this paper Phase 2 experience on Page -- starting on Page 100.

A. Yes.

Q. And he talks about a Canadian study starting dose of 600 that was reduced to 500 milligrams per dose --

A. Yes.

Q. -- after. And he reports that, what, it was five of the first eight patients that had to be reduced from 600 to 500 milligrams?

A. Yes.

Q. And he reports that -- an overall response rate of 20 percent. Do you see that?

A. Yes.

Q. What is that referring to?

A. (No response.)

Q. So would one of skill in the art consider a 20 percent response rate to be acceptable in a Phase 2 trial?

A. It's quite interesting at the time, yes. It depends on the disease. In lymphomas, it wouldn't be particularly exciting, but in a solid tumor like this, where there are not many other effective therapies, it's really worth

pursuing. Yes.

Q. I show you what's been marked as Lilly Exhibit 2030.

(Lilly Exhibit 2030 incorporated by reference.)

Q. This is the Rinaldi paper.

A. Mm-hmm.

Q. And you -- I think you referred to it as Rinaldi II in your declaration.

A. Right.

Q. And in the abstract, Rinaldi refers to toxicities that are manageable and reversible. Do you see that?

A. Mm-hmm. Where is it?

Q. In the -- in the abstract.

A. In the abstract.

Q. Yeah.

A. Okay. Mm-hmm.

Q. And this is a report of a Phase 1 trial of pemetrexed?

A. Right.

Q. Okay. And he says, "Given that toxicities were manageable and reversible...", do you see that?

A. I do.

Q. All right. What does "reversible" mean?

A. That by the time you're ready to give the next dose, whatever toxicity has occurred has gone away and you're back to baseline.

Q. And how does -- and by "reversible," is that a reference to stopping treatment with the drug?

A. No. It just means that if you have an abnormal creatinine, it's come back to baseline. It doesn't mean that it's not going to happen again, but --

Q. Doesn't "reversible" mean to one skilled in the art that you can fix it by stopping administration of the drug?

A. No. Not -- no. I mean, it's a broader term than that. I mean, when you talk about reversible toxicities, it means that when the drug is stopped, it goes away, but you can readminister the drug for the next cycle. There are many examples of that.

Methotrexate causes liver enzyme abnormalities during treatment with high-dose methotrexate. But they come back to normal, and you give the next cycle. And the same thing

happens, and you give the next cycle. And there's no permanent damage.

Q. Right. So if you're observing a toxicity that is reversible while you're administrating the drug, you reverse it by stopping the drug?

A. Well, most chemotherapy is not given continuously. It's given intermittently. So you give it. Toxicity occurs. It reverses. It comes back to normal. You give it again. So for an oncologist to say toxicity is reversible means that the toxicity isn't permanent.

Q. So would a Grade IV toxicity be considered reversible?

A. Yeah. It can. Often the marrow toxicity can be Grade IV and it's reversible. Many of the regimens we give, for example, with high-dose chemotherapies for various diseases, that happens every cycle, Grade IV toxicity.

Q. And patients can also die from a Grade IV toxicity?

A. They can. But we've learned how to manage those things. That's part of the reason we have fellowships in oncology so we know what we're doing.

Q. And in the June 1999 time frame, one of ordinary skill would understand that a Grade IV toxicity, although perhaps reversible, could also be fatal?

A. It could be. Yeah. Absolutely. It could be.

Q. Now, Rinaldi has a table, Table 2 on Page 83, at the bottom. Are you there?

A. I am.

Q. And it's real straightforward. Does he label toxicities ranging from zero to four?

A. Yes. That's the grade.

Q. Was that a recognized grading system in June of 1999?

A. Yes.

Q. All right. And can you, at a very high level, take me through what zero to four, what each grade level means?

A. Well, it's an NCI system that was developed for the trials they sponsor and it's been widely adopted, and it changes over time.

Zero means there's no toxicity. One is a very minor toxicity, which is probably not much, if any, clinical significance. Two is a toxicity which is a moderate toxicity which, again, is

usually something that doesn't change therapy. Grade III toxicity is a serious toxicity involving either an organ or bone marrow. And Grade III toxicity in an organ, if you get it frequently enough, you may have to change your schedule or administration or dose. And Grade IV toxicity in the marrow has the same connotation as Grade III toxicity elsewhere.

Q. And as a treating physician, would one of ordinary skill in the art in June of 1999 --

A. Yeah.

Q. -- want to reduce or minimize the occurrence of Grade IV toxicities?

A. Depending on the result you're getting with the drug. If you're getting a very good result in a tumor that's not otherwise treatable, you would tolerate, you know, a 10, 15 percent incidence of Grade IV toxicity to get the 35 percent response rate that you get with Alimta and platinum in nonsmall cell lung cancer.

Q. Now, on Page 84 of Renaldi, on the left-hand column, the last paragraph --

A. Yeah.

Q. -- he notes that what you get there is a statement two of these five experienced

Grade IV neutropenia?

A. Mm-hmm.

Q. Do you see that?

A. Where is this, now?

Q. On the left-hand side.

A. Of 87?

Q. On Page 84.

A. Oh, 84. I'm sorry. Okay. This is under the weekly times four schedule, or which schedule is it?

Q. It's the paragraph that starts at "the initial dose level of 10 milligrams."

A. Yes. That's weekly times four. Okay.

Q. And he goes on. And about a little over halfway down -- well, he says, "After the first patient developed Grade IV neutropenia, five additional patients were treated at this dose level. Two of these five experienced Grade IV neutropenia" --

A. Sure.

Q. -- "which prompted a deescalation" --

A. Right.

Q. -- "to 20 milligrams."

So he lowered the dose.

A. That's right. This was not 10 percent

of the patients. This was 100 percent of the patients. So that's -- this is a dose-finding study, and, you know, that's too much.

If 100 percent of your patients are getting Grade IV neutropenia, you stop, unless you're treating leukemia.

Q. So in response to this Grade IV toxicity we're seeing, he lowered the dose with these patients?

A. If it's in 100 percent of your patients, absolutely.

Q. And one of ordinary skill in the art would understand, in the June of 1999 time frame, that patients could experience unacceptable toxicity?

A. With this drug?

Q. Yes.

A. Occasional patients could. I would add that this is a schedule that they dropped because the other one was safer and more effective.

Q. Now, so I'm still at Page 84. We have the statement, "After the first patient developed Grade IV neutropenia, five additional patients were treated at this dose level."

A. Right.

Q. And that was a 40-milligram dose. Correct?

A. Wait a minute. I've got to find it now. Where is this?

Q. Page 84. Page 84.

A. Which paragraph?

Q. All right. The paragraph that starts out "the initial dose level."

A. Yes.

Q. Okay. If you go down a little bit, it says, "The next patient who received 20 milligrams also experienced no significant toxicity. So the dose was escalated to 40 milligrams."

Do you see that?

A. Yes.

Q. So there was a first patient, then, that was administered a 40-milligram dose. Correct?

A. Right.

Q. And then five additional patients were treated at 40 milligrams. Correct?

A. Right.

Q. So we've got a total of six patients that are treated at 40 milligrams. Correct?

A. Yes.

Q. And of those six patients, two of them experienced a Grade IV toxicity at 40 milligrams. Right?

A. Yes.

Q. So they deescalated those two patients to 20 milligrams. Right?

A. That's entirely consistent with the way we do Phase 1 studies. Two of six. And then you -- that's -- that calls for a dose reduction. One of three, you go to expand the number to six. And when you get two of six, you don't -- you don't go further.

Q. And so the two of these six patients at 40 milligrams experienced unacceptable toxicity. Is that correct?

A. Pardon? Two of six.

Q. Two of the six.

A. Yeah. And that's consistent with the way we do dose escalation or deescalation in a Phase 1 trial.

Q. And if you go up to the first page, the abstract -- well, not the abstract, the first page, column on the right --

A. Right.

Q. -- there's a statement, "The maximum tolerated dose (MTD) was defined as that dose level at which 30 percent of the patient population developed unacceptable toxicity."

Right?

A. Right.

Q. Is that what you're referring to?

A. Well, it's -- defining the MTD requires more than six patients. But if you have 30 percent of the patients developing unacceptable toxicity, that would call for a dose -- a deescalation. But that's drug-related, severe toxicities.

Q. Okay. And so --

A. That's Grade IV neutropenia.

Q. Okay. So in June of 1999, this maximum tolerated dose, MTD, the general rule of thumb was that the maximum tolerated dose would be that dose at which 30 percent of the patient population develops unacceptable toxicity?

A. Right.

Q. Okay. Now, how does that compare in practice to FDA-approved drugs? What level of unacceptable toxicity is tolerated for an FDA-approved drug?

A. It varies. With the new checkpoint inhibitors we're using, virtually everybody gets unacceptable toxicity. But they come out of it, a fraction of them, cured. And, you know, that happens, and it depends on the benefit.

Q. And in June of 1999, though, was there a rule of thumb of the acceptable toxicity for an FDA-approved drug?

A. I think, again, it varied. For example, in June of 1999, we were doing marrow transplants, every patient got Grade IV neutropenia. The drugs that were used in marrow transplant were still approved, but -- and those schedules were acceptable.

It depends on what the therapeutic result is and the clinical situation. If you're treating with a single agent and you don't expect a great benefit, you wouldn't want that kind of toxicity. But if you're treating in a situation where you're going to cure people, you would accept that toxicity.

Q. Now, on Page 85, Rinaldi reports -- he says -- and I'm on the right-hand side, last full paragraph, about six lines from the bottom, "This nephrotoxicity appeared to be reversible and

nonprogressive despite continued treatment in most of the patients."

Do you see that?

A. I do.

Q. That's a reference to kidney toxicity?

A. Right.

Q. And so what Renaldi II is reporting that renal toxicity, at least in this study, was not of particular concern with pemetrexed?

MR. GROSSMAN: Objection to the form of the question.

A. It is a concern in the sense this is a drug which depends on renal function for excretion. So if you're giving the drug and you get renal toxicity from it, you're not going to have normal pharmacokinetics.

And I could explain the pharmacokinetics, if you want. This is something that we see with a lot of cancer drugs, and we have to dose reduce or alter doses. So it doesn't mean that you can tolerate this. It makes it risky.

Q. He reports, though, that this kidney toxicity is reversible, though.

A. That's right. So at the next cycle, it's normal again.

Q. It could be fixed.

A. But then the next time you give the drug, the renal function deteriorates, pharmacokinetics are likely to change with that deterioration as you get -- as you try to eliminate the drug.

So it creates a problem for the drug which is renal. And if this were a drug that was metabolized by the liver, it wouldn't be -- I wouldn't be that concerned about it. But I am concerned because of the fact that this is a -- this is a drug which depends on renal function for its excretion.

Q. But the authors in this paper, Rinaldi, they don't -- they don't report to one of ordinary skill in the art that you should cease using this drug because of kidney toxicity?

A. No. You wouldn't cease using it. No.

Q. They weren't abandoning this drug based on any concerns?

A. Well, they did change the dose. They want back to 500.

Q. For reasons other than kidney toxicity?

A. I don't know. It's hard to say, because they were seeing renal dysfunction at

doses higher than 500 and they were seeing toxicity, and they felt that they were safer going with a dose of 500. We really don't know that.

I mean, unfortunately, they didn't do the pharmacokinetic studies that would help us understand that.

MR. GABRIC: I show you what we've marked as Exhibit 1070.

(Excerpt from the May 16-19 Annual Meeting of the American Society of Clinical Oncology marked Exhibit 1070.)

BY MR. GABRIC:

Q. And I want to focus on the abstract 1307. It's a Phase 2 -- it's on the lower left-hand portion of Page 339A. It says, "a Phase 2 study of the multi-targeted antifolate MPA," which is pemetrexed. Do you see that?

A. I do.

Q. Is Paz-Ares is the person --

A. He was a fellow with me.

Q. Sorry?

A. He was one of my fellows.

Q. Okay. How do you pronounce that?

A. Paz-Ares.

Q. Paz-Ares. Thank you.

A. Yes.

Q. Now, this abstract, this is a study of -- it's a Phase 2 study of pemetrexed. Right?

A. Yes.

Q. Okay. And the first six patients started out at a 600-milligram dose of pemetrexed. Right?

It says, a few lines down, "MTA was administered as ten-minute infusions every three weeks at a dose of 600 milligrams per six patients."

A. Right.

Q. "Or 500 milligrams subsequent patients"?

A. Right.

MR. PERLMAN: Milligrams per meter squared.

MR. GABRIC: Yeah. Understood. Understood.

Q. And so does this abstract report the reason why these -- the starting dose was taken down from 600 to 500 milligrams meters squared?

A. Toxicity.

Q. Okay. And then there were a total of

18 patients that were evaluated?

A. Yes.

Q. Okay. And eight patients, or 44 percent of the patients, had a Grade III neutropenia toxicity?

A. Yes.

Q. And five patients, or 28 percent, had a Grade IV neutropenia toxicity. Correct?

A. Yes.

Q. So 72 percent of the patients in this study had a Grade III or Grade IV neutropenia toxicity. Correct?

A. Let me see, I have to find where you're talking -- where you're reading. Six patients had a partial remission. Wait a minute. Oh, I see it. Yes. Well, it could have been the same patient, different cycles. We don't know.

In other words, they don't tell us that these are individual patients. You know, in other words, on cycle one, they could have had Grade III and cycle two they could have had Grade IV. I'm not sure.

Q. Did --

A. But it's -- it's a relatively high rate. And that's why -- I think that's one of

the reasons they reduced the dose.

The other thing you have to understand about transitional cell cancers are -- depending on the way it presents, it may present with renal obstruction, in which case, renal function isn't normal. So this is a higher-risk population than the lung cancer patients.

Q. And at the end, the abstract offers a conclusion. It says, "In conclusion, MTA pemetrexed has definitive antitumor activity in advanced TCC of the bladder, but its toxicity is significant"?

A. Is significant. Yeah.

Q. One of skill would have understood that in June 1999?

MR. GROSSMAN: Objection to the form of the question.

A. I think that a person would understand that toxicity was significant. Sure. That doesn't mean that we wouldn't use the drug. And I think the approach would be to dose reduce in relationship to renal function, which they didn't do.

MR. GROSSMAN: We've been going for about an hour. Can we take a break?

MR. GABRIC: Yeah.

(Discussion off the record.)

THE VIDEOGRAPHER: The time is 3:27. We're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: Here begins Disk 6 in the deposition of Bruce Chabner, M.D. The time is 3:44. We're on the record.

BY MR. GABRIC:

Q. Welcome back, Dr. Chabner.

A. Nice to see you.

Q. In your declaration, you talk about another alternative to treating antifolate toxicity, and that's using something known as G-CSF?

A. Yes.

Q. And I show you Exhibit 1071.

(Drugs@FDA printout regarding Neupogen marked Exhibit 1071.)

Q. Is Neupogen a G-CSF?

A. It's one of them.

Q. And Neupogen was a --

MR. GROSSMAN: I'm going to object to this document. There's no indication that it's prior art.

MR. GABRIC: Objection noted.

Q. And just to give you context, we printed this off the FDA website, Exhibit 1071. And it -- and my question: Was Neupogen one of the G-CSF agents available to one of skill in the art in June 1999?

A. Yes. I believe it was.

Q. And were there any others available in 1999?

A. I think GM-CSF was available.

Q. I'm sorry?

A. GM-CSF.

Q. GM-CSF?

A. Yes.

Q. What is that?

A. Different. It does the same thing, but it's different. Different molecule.

Q. I want to focus on your declaration. Did your declaration address GMSF [sic]?

A. GM-CSF? I don't remember whether we talked about granulocyte colony stimulating factor or G-CMF or just the general category of colony stimulating factors.

Q. Okay. I want to talk about G-CSF.

A. Okay.

Q. All right? Other than Neupogen, were there other G-CSF agents available in June of 1999?

A. GM-CSF.

Q. What is the difference between the two?

A. They're totally different molecules. They're large proteins, they have different receptors and they stimulate a different set of receptors. But both of them raise the white count.

Q. Okay. And, in your opinion, is Neupogen one of the agents that one of ordinary skill in the art would have considered for reducing toxicity of an antifolate in June of 1999?

A. I believe so. You know, I don't have the approval date for it, but I believe it was available then. Oh, there it is. In 1991. Yes.

Q. Now, does Neupogen impact any hemopoietic lineages other than neutrophils?

A. It's basically a granulocyte stimulating factor. GM does -- has broader activity. But G-CSF is pretty much confined to neutrophils. I don't think it has much other effect.

Q. And in the 1999 time frame, do you know how Neupogen was administered?

A. Subcutaneously.

Q. Does that mean by injection?

A. Yes.

Q. And how frequently was it administered in the June of 1999 time frame?

A. It was given for several days. There are other forms of it. There's a long-acting form, Neulasta, which came out, which you only needed one injection. It lasted a longer period of time.

Q. And let me show you the product insert for Neupogen, marked as Exhibit 1072.

(Product insert for Neupogen marked Exhibit 1072.)

A. Is this our exhibit?

Q. Pardon me?

A. Is this our exhibit?

Q. It's a new exhibit.

A. Okay.

Q. And if you turn to Page 23, there's a "Dosage and Administration" section on Page 23.

A. Mm-hmm.

Q. And in the second paragraph, it says,

"Neupogen should be administered daily for up to two weeks."

Do you see that?

A. Yeah. But you give it until the white count comes up. The white count usually came up in two or three days, four days, maybe.

Q. So depending how quickly the white count comes up, that would dictate --

A. Yeah. You don't give it two weeks.

Q. What if the white count didn't come up for a week or eight days?

A. That was rare. That's rare with these drugs.

Q. What the label is saying, that you do it daily for up to two weeks?

A. Yeah. But what I'm telling you is you don't -- rarely you have to give it for two weeks. In fact, I would be very worried about the patient's bone marrow if I had to give it for two weeks.

MR. GROSSMAN: Counsel, is this prior art? Is this the version available by June 2000? There's no --

MR. GABRIC: It's certainly our intent. But I can't make any representation right now.

MR. GROSSMAN: Okay. Then I have an objection to the document. It's just sort of a printout. It's not clear where it's from.

MR. GABRIC: If you look -- if you look at Page 27, there's an issue date. April 2, 1998. We made every effort. I believe it is the prior art version.

MR. GROSSMAN: So I still have an objection.

MR. GABRIC: I understand.

MR. GROSSMAN: It's just a printout. I'm not sure where it's from. But go ahead.

MR. GABRIC: Your objection is noted.

MR. GROSSMAN: It hasn't been cured.

BY MR. GABRIC:

Q. Do you have any experience in administrating Neupogen?

A. Yes.

Q. All right. Does this package label seem to be from the pre-1999 time frame?

A. I guess it does. You know, you're asking me a very hypothetical question. Right?

Q. There's nothing jumping out at you --

A. I don't know.

Q. -- saying this can't be prior to 1999?

A. I don't know. I don't know. I mean, there's 17 years of experience. I think there's one thing in here, which is there's a caution, you know, that other tumor -- other kinds of tumors, particularly myeloid tumors, might have receptors that respond to this. And that's in here because the experience of Amgen with erythropoietin, where there was evidence of tumor progression with erythropoietin, which is a separate molecule. So they're protecting themselves here. Amgen went through total hell with their EPO business. So I have a feeling this was written after that happened.

Q. And when did that happen?

A. Oh, about ten years ago.

Q. So you think the date on here is wrong?

A. What's the date?

Q. The date on Page 27 is April of --

A. I thought this was downloaded today.

Q. April -- the issue date is on Page 27, April 2, 1998. There's a copyright date of 1991 through 1998.

A. Well, they might have still been concerned. The fact is you've downloaded it today. I don't know when it was written or

revised.

Q. All right. So but it's your opinion in June of 1999, one of ordinary skill in the art would have considered Neupogen as a means to reduce toxicity in an antifolate. Correct?

A. Yes.

Q. And who would administer the Neupogen? Would it be the physician, or the patient gives it to themselves?

A. No. Patients don't give it. I'm not sure whether it can be given by patients themselves now. I don't think so. I think it's -- we administer it in the outpatient clinic routinely.

Q. Are there some patients that would self --

A. I don't know. I can't say.

Q. And do you have a sense for the cost of Neupogen in the June of 1999 time frame?

A. No.

Q. More expensive than Vitamin B12?

MR. PERLMAN: To whom?

A. You know, I told you, I don't know what the costs are. Right?

Q. And if you look on Page 14, it says,

"potential effect on malignant cells."

A. Yes.

Q. It says, "The possibility that Neupogen can act as a growth factor for any tumor type cannot be excluded." Right?

A. Well, as of 216, there's no evidence for this.

Q. As of when?

A. 2016.

Q. Yeah. But as of June of 1999 --

A. There was no evidence for that either.

Q. But this is a caution to one of ordinary skill in the art that could possibly act as a growth factor for a tumor. Right?

A. But there was no experimental evidence for that. There were -- there were some constructs of cells which had the G-CSF receptor that they made into responsive cells that could be stimulated. But I don't know of any evidence, with the possible exception of AML, where that could happen. And there was no evidence then and now that solid tumors would be stimulated by it.

Q. So notwithstanding this statement about the potential effect on malignant cells, one of ordinary skill in June of 1999 would -- would

administer Neupogen -- Neupogen as a means for addressing toxicity in an antifolate. Is that correct?

A. Yes. And despite that, it was extremely widely used, and still is today.

Q. And so I just want to understand something, though. Your opinion is one of ordinary skill in the art would take this cautionary statement with a grain of salt because there was no citation to evidence?

A. Well, that's right. I mean, both you and I look at evidence when we make decisions about things. If there's no evidence that that happens at that point, and you're faced with a patient whose white count is low, you give it.

Q. And do you know when Neulasta was approved?

A. Sometime afterward.

Q. Sometime after June of 1999?

A. Yes.

Q. In fact, it was sometime in the 2000 time frame?

A. Yes.

Q. I think it was 2002. Does that sound about right?

A. Yeah.

Q. I show you what's been marked as Lilly Exhibit 2040.

(Lilly Exhibit 2040 incorporated by reference.)

Q. This is the Smith paper that's referred to in your declaration. Right?

A. Yes, it is.

Q. Okay. And it's your opinion that a person of ordinary skill in the art in June of 1999 would also consider leucovorin rescue rather than -- instead of folic acid to treat toxicity of pemetrexed?

A. For an antifolate?

Q. Yes.

A. Yes.

Q. And leucovorin rescues -- I'm sorry, leucovorin rescue is used after administration of the antifolate. Correct?

A. Yes. It's used a day or two afterward.

Q. Are you aware of -- would anyone have -- strike that.

Would a person of ordinary skill in the art in June 1999 be aware of anybody pretreating with leucovorin?

A. Well, in experiments they did, but I don't know of anyone clinically that did. Maybe. Let's see what he did here.

Okay. Fine. Yes. He didn't use leucovorin. He used folic acid. Oh, he did use leucovorin.

Q. So this is a study --

A. Actually, he didn't show that leucovorin was much more effective in reversing toxicity.

Q. This is a study that was done on an antifolate called 1843U89. Right?

A. Right.

Q. And that's a TS inhibitor. Correct?

A. You know, I don't know much about this drug. I think it had a very short and unhappy history in the clinic.

Q. But this paper was available to one of ordinary skill in the art --

A. Yes, it was.

Q. -- in June of 1999?

A. Yes.

Q. And I'd like to turn to Page 6122.

(Witness complies.)

A. Okay.

Q. I'm sorry. I'm on the wrong page. 6123. And he's reporting here on the effect of folic acid and leucovorin on this antifolate 1843U89. Right?

A. Yes.

Q. And he reports here that folic acid and, to a lesser extent, leucovorin do not efficiently reverse cytotoxicity of 1843U89. Correct?

A. Right.

Q. So what he's reporting here is that leucovorin reduced the efficacy of this antifolate more than folic acid did. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. I'd have to take a look at the graph to actually understand it.

Whoa. You know, this is really hard to decipher because the key to the graph is not correct. It's got two black spots here in Figure 9, and there is one black line and one gray line, and there's no indication of what the gray line is. Do you see what I mean?

Q. No. What figure are you referring to?

A. Figure 5. So what's -- what's the gray

bar standing for? I'm unable to find it in the legend.

Q. This document is cited in your declaration. Correct?

A. Yeah. But you're questioning me about it. I'm asking you. You're asking me to interpret it, and I can't read the document.

Q. Do you think there's an error in the figure?

A. Well, I think it's not copied correctly. I don't know.

Q. And this is the --

A. There are two black things that are marked black here. There's only one black bar. I imagine that third bar, rather than being black, is gray, is the result after a dose of folic acid.

Q. So I'm sorry. You're assuming that the gray bar on the far right corresponds to the oral dose of folic acid on days three through --

A. That's right.

Q. -- seven --

A. I think that's what it is.

Q. -- post-implant?

A. Yeah. I just can't tell. I don't

know. Maybe it's -- maybe it's the other one. Untreated animals would have the largest bar. Tumor volume would be greatest. The second is animals treated with the drug alone. And the third is probably the animals treated with the drug plus folic acid. That's what I'm assuming.

Q. Okay.

A. And the animals treated with drug plus folic acid have a larger volume than the others. But there are no arrow bars here.

So it says P.917, no difference at day ten and P.043 at day 21. I assume they're -- I don't know what they're comparing here, whether they're comparing -- what to what. They're comparing everything to the untreated animals or comparing everything to the -- I guess my conclusion here would be that folic acid seems to reduce -- allow some reduction in tumor volume on day 21.

And my conclusion is also that the interval between folic acid administration and drug was not sufficient for the metabolism of folic acid to a usable kind of folate. But it was -- it did allow folinic acid to be converted, which allowed it to rescue both the tumor and probably animal as well.

Q. Okay. So let me -- let me ask you this. If you look on Page 6123 -- and this is a document cited in your declaration --

A. Yes.

Q. -- that we got from Lilly.

A. Unfortunately. Yes. Do you see what my problem is?

Q. I'm not following you completely. But I'm going to take your word for it that you have some confusion with the figure.

A. That's right.

Q. Okay. And so let's focus on the text real briefly.

A. Okay.

Q. On 6123, on the left-hand side where it says "by contrast," do you see that?

A. Yes.

Q. "By contrast," 183 -- I'm sorry -- "1843U89 and its diglutamide are strong noncompetitive inhibitors of the target enzyme TS." Correct?

A. Yes. Right.

Q. And he goes on to report, "As such, the reduced folate substrates generated in cells for folic acid or leucovorin do not compete for

1843U89 binding to TS."

Do you see that?

A. Mm-hmm.

Q. Okay. And that's what he's reporting to one of ordinary skill in the art as of June of 1999?

A. Yes.

Q. Then he goes on to say, "Thus, folic acid and, to a lesser extent, leucovorin do not efficiently reverse cytotoxicity of 1843U89."

A. Right.

Q. Right?

A. Well, we're dealing here with a noncompetitive inhibitor. That means that it will bind very tightly and it won't be competed off by folates. And that's a different thing than pemetrexed, which is a competitive inhibitor, which is very susceptible to competition from the folates.

Q. And he's reporting here that leucovorin had a greater detrimental impact on this antifolate --

A. Yeah.

Q. -- than folic acid did?

A. Yeah. Well, I pointed out that he

probably didn't get much reduced folate. So there would probably be some -- if there's any off rate, there will be a little activity with leucovorin. But it's basically a different drug than pemetrexed. It's a noncompetitive inhibitor.

Q. But like pemetrexed, this antifolate is a TS inhibitor.

A. Right. It is. It's inhibiting the same site, but it's not competitive. It's not a competitive inhibitor.

Q. Competitive inhibitor with what?

A. With the folates. It's not competing with the folates. It's attaching. And a folate, once it attaches, is not going to drive it off.

Q. And that's with respect to the TS enzyme?

A. Yes.

Q. Now, this paper also refers to DDATHF on Page 6122, under the "Discussion" section, second paragraph.

A. Yes.

Q. Is that lometrexol?

A. That's dideazatetrahydrofolic acid. I don't think it is. I think it's a GARFT

transformylase inhibitor. Yes, sir. A GARFT -- I don't think that's pemetrexed. It's a different drug.

Q. What about the reference to T-O-M-U-D-E-X. Do you see that?

A. Tomudex is a folate-type TS inhibitor.

Q. Is that raltitrexed?

MR. GROSSMAN: Raltitrexed.

A. Raltitrexed. I think it is. And that's one that is sensitive to folate competition. Yeah. That's what it says here. They rescued.

This compound is an unusual TS inhibitor in the fact that it's noncompetitive. I just, unfortunately, don't remember the structure, actually. It probably is given here. Let me see.

MR. GABRIC: We're ready to move on, Doctor. Unless you have any burning desire to discuss this further.

THE WITNESS: No. I'm interested in it. But Burroughs Wellcome had a program in folates as well as Lilly.

Q. I show you Lilly Exhibit 2033.

(Lilly Exhibit 2033 incorporated

by reference.)

A. Sure.

Q. It's the Quinn paper. It's discussed in your declaration. And it's your opinion that one of ordinary skill in the art would consider using betaine -- or I'm sorry. We've been through this.

A. Betaine.

Q. Beta --

A. Betaine.

Q. And it's your opinion one of ordinary skill in the art would consider using betaine to lower homocysteine levels in the June 1999 time frame, from the point of the Quinn reference. Right?

A. Yes.

Q. And Quinn talks about counteracting the cytotoxic effects of methotrexate. Correct?

A. It's specifically talking about the point of counteracting the possible toxicity of homocysteine elevation.

Q. And he's not addressing pemetrexed.

A. Well, it is. It's -- it's related to an antifolate. But it's not pemetrexed specifically. That's right. But it's really

discussing how you deal with a -- a -- with homocysteine, how -- the potential ways in which you can lower homocysteine levels.

Q. And Quinn is talking about using betaine post treatment to rescue patients?

A. Well, I guess it would be post treatment. Or it might be pretreatment. If you had measured homocysteine levels and you were worried, you might use it pretreatment.

Q. Quinn used it post treatment.

MR. GROSSMAN: Objection to the form of the question.

A. I don't think he ever used it. He didn't.

Q. So we've talked about dose and scheduling adjustments as something that one of ordinary skill in the art would consider in addressing the toxicity of pemetrexed. Right?

A. Yes.

Q. And dose reductions can impact the efficacy of an anticancer agent. Right?

A. Yeah.

Q. And changing the schedule can impact the efficacy of an anticancer agent?

A. It could.

Q. One of ordinary skill in the art would understand that in June of 1999. Correct?

A. Yes.

Q. And, in fact, one of ordinary skill in the art in June of 1999 would have understood that any rescue strategy could impact efficacy of an anticancer agent?

A. Well, that's true. There are some well-proven ones that didn't seem to interfere with drug activity, the most prominent being leucovorin rescue, which was used widely in cancer, all sorts of cancers, and didn't affect antitumor activity.

Q. But one of ordinary skill in June of 1999 would have understood that a general problem with a rescue strategy as a whole is it could have a negative impact on efficacy.

A. Well, I don't -- I don't think a person of ordinary skill would generalize. Certain things we know and certain things we guess at or we base -- are more hypothetical.

What we do know is that using leucovorin didn't impact on the efficacy of methotrexate. And what we also knew is that folic acid and B12, there was evidence that it would reverse drug

activity and -- and -- and cause tumor progression.

So, you know, you're balancing a lot of different thoughts here. And the reasonable course of action is to use leucovorin rescue.

Q. Now --

A. Or -- and I also think -- we haven't gone into this, but there's a rationale for dose reduction, too. If a person is folate deficient, we know from Worzalla, the studies that you quoted, that folate-deficient mice were very sensitive to the drug and that you could actually produce the same 100 percent inhibition rate with much lower doses of folate.

So that would be consistent with the idea that you could reduce folate -- reduce pemetrexed in those patients without sacrificing activity.

The second factor is that in toxic patients -- some of the toxicity is related to differences in pharmacokinetics of the drug. Some patients just don't clear the drug as fast. So by reducing the dose, you basically normalize the drug level.

Q. Take a look at your trial testimony.

A. Sure.

Q. I want you to go to Page 1221.

(Witness complies.)

Q. Again, Page 1221 --

A. Mm-hmm.

Q. Will you let me know when you get there?

A. I am.

Q. Go to Line 24.

A. Yup.

Q. You were asked a question:

"QUESTION: Dr. Chabner, you agree that all rescue strategies could have a negative impact on efficacy as a chemotherapy agent, right?

"ANSWER: That's correct."

A. Yeah.

Q. You gave that testimony. Right?

A. Yes.

Q. And you stand by that testimony?

A. I do. And it says and "potential negative impact," negative impact.

Q. And one of ordinary skill in the art would have understood that in June of 1999?

A. Yeah. But some we know much more about than others. Right?

Q. I show you Exhibit 1005.

(Sandoz Exhibit 1005 incorporated by reference.)

BY MR. GABRIC:

Q. It's the '974 patent. And this is a document you referred to in your declaration. Correct?

A. Right.

Q. When did you become aware of the '974 patent, first of all?

A. Well, I was certainly aware of the drugs. And I assume they were patented. So I didn't read the patent until this case came up.

Q. Sometime after 2006 or '7 or '8 time frame?

A. Yes. Yes. Yes.

Q. Now, there's a formula at Column 3 of the '974 patent.

A. Which page is it?

Q. Column 3. There are columns at the top. Column numbers at the top. Just turn the page.

A. Oh, I see what you mean. I got it. I got it. Okay.

Q. And you state in your declaration that you understand that pemetrexed is technically

covered by this structural formula. Right?

A. Right.

Q. Okay. And the '974 patent reports at Column 1, starting at Line 47 --

A. Yes.

Q. -- it says, "We have now discovered that the toxic effects of lometrexol and related GARFT" -- GARFT --

A. GARFT transformylase.

Q. Just call it GARFT transformal [sic] inhibitors.

A. GARFT transformylase inhibitors.

Q. Transformylase inhibitors -- we'll just call it GARFT, if you're okay with that.

A. Yeah.

Q. -- "and other antifolate agents which bind to folate-binding protein can be significantly reduced by the presence of an FBP binding agent without adversely affecting therapeutic efficacy."

Do you see that?

A. I do.

Q. And then at Column 2, Lines 28 through 46, take a moment to take a look at that.

A. Yes.

Q. And I'm focused on Line 43 or 42 or 43, where it says, "Any compound which is shown to inhibit the GARFT or other folate-required enzyme is subject to treatment in accordance with this invention."

Do you see that?

A. Yes.

Q. So this patent is not limited to only compounds -- or to compounds that only inhibit GARFT. Correct?

A. That only inhibit GARFT. Right. Well, I think it's intended for that series of compounds and those that have -- that use the -- that can bind to the folate-binding protein. I'm not a patent lawyer. So you'd have to tell me what it actually covers.

Q. Well, one of ordinary skill in the art reading this passage would understand that this patent is meant -- devoted to inhibitors that are exclusively GARFT inhibitors?

A. I think what my -- you've asked my interpretation. I think that it would require that the mechanism of toxicity is related to GARFT inhibition. Because if it were -- you know, if it had weak activity in GARFT but very

strong activity against another site, then it probably wouldn't make any difference if all this happened.

Q. Well, isn't it true, Doctor, that the '974 patent nowhere says that the teachings in this patent are limited to primarily GARFT inhibitors?

A. You're right. But as I said, I'm not a patent lawyer. So your opinion on this probably counts more than mine.

Q. And the patent states that the teachings apply to things that inhibit GARFT or bind folate-binding protein agent. Right?

A. I don't think it says "or." Does it say "or"? Does it say "and"? Oh, it does say "or." So "binds to the folate-binding protein" would be covered.

Q. And where are you looking?

A. On the bottom.

Q. Bottom of Column -- Column 2?

A. Yes. Which is rather strange, because folic acid and other things that are not anticancer drugs are -- bind to the folate-binding protein. So that's sort of hard to understand.

Q. So the patent says, "Other GARFT inhibitors and antifolates are also included with within the scope of this invention, and such compounds can be determined by routine evaluation of either their ability to interact with and inhibit the subject enzyme or to bind to FBP," which is folate-binding protein. Right?

A. Yeah. I guess that's right. So it would cover antifolates that bind to the folate-binding protein, but does it cover antifolates that don't bind to GARFT? That's what -- I'm trying to figure that out.

Q. And one of ordinary skill --

A. Okay.

Q. -- in June of 1999 would understand that pemetrexed binds to GARFT. Correct?

A. Right. It's actually the polyglutamates that bind to GARFT.

Q. And one of ordinary skill would have understood that in June of 1999?

A. I think so.

Q. And that's the polyglutamate of pemetrexed?

A. Right.

Q. And one of ordinary skill in June of

1999 would have understood that pemetrexed also binds to folate-binding protein. Right?

A. Yeah. It wasn't -- it weakly binds to it. Yes.

Q. And one of ordinary skill in the art in June of 1999 would have understood that pemetrexed is a potent inhibitor of GARFT. Correct?

A. That's a hard question. The potency is a hard question to answer. It certainly -- it does bind and inhibit GARFT, but in the relative potency with other GARFT binding agents, it's rather weak.

Q. Can you turn to Page 1297 of your prior trial testimony.

A. Yes.

(Witness complies.)

Q. And I'll refer you to -- I refer you to Line 2. And you were asked the following questions:

"QUESTION: And so you and your coauthors wrote" -- this is a paper you wrote apparently -- "that pemetrexed is a potent inhibitor of GARFT, correct?

"ANSWER: Yes. It's not as potent as it is

against TS. The data which you're familiar with shows that.

"QUESTION: But it is a potent inhibitor of GARFT, right?

"ANSWER: Yes. It's submicromolar.

"QUESTION: And that's potent?

"ANSWER: Yeah. I think at this time, it would be regarded as a reasonable potency."

Then you go on, "I can put that in context. A drug like methotrexate has..." Then you trail off.

A. Yeah.

Q. And so you stand by that testimony?

A. That's exactly what I told you. I said it was a -- as a polyglutamate, it's a reasonably potent inhibitor, but the other drugs are ten to 100 times as potent. And I hope that answers your question.

Q. And one of ordinary skill in the art would have understood it was a reasonably potent inhibitor of GARFT?

A. Yes. Yes.

Q. In the June 1999 time frame.

A. Yes. But not in the same class as the ones that were directed solely at GARFT.

(Discussion off the record.)

Q. Let me just ask you. This in June of 1999, the time frame, would one of ordinary skill in the art have understood that pemetrexed is efficiently transported by folate-binding protein?

A. Would you repeat that, please.

Q. Would a person of ordinary skill in June of 1999, would they have understood that pemetrexed strongly bound to folate-binding protein?

A. It binds to folate-binding protein. Exactly how well it's transported I don't think was clear. There are papers saying that the predominant transport mechanism was the reduced folate carrier. It certainly did bind. Yes.

Q. I'm showing you what we've marked as Exhibit 1073.

(Deposition transcript of Bruce Chabner, dated April 23, 2013 marked Exhibit 1073.)

BY MR. GABRIC:

Q. For the record, it's a book that includes -- includes a paper that you coauthored on antimetabolites.

A. On antimetabolites. That's right.

MR. GROSSMAN: This is already marked as an exhibit, and I only note that because there tends to be total confusion if documents are the same exhibit.

MR. GABRIC: Is it our exhibit?

MR. GROSSMAN: It's both of them.

MR. GABRIC: We think it's a different year.

MR. GROSSMAN: Okay. I'm fairly certain this is also Exhibit 2074.

MR. GABRIC: It's what?

MR. GROSSMAN: Exhibit 2074.

MR. PERLMAN: Why don't we do this: Ask your questions. At a break, we'll figure it out.

MR. GABRIC: Sounds good.

MR. PERLMAN: Does that work?

MR. GABRIC: Yeah. That works.

BY MR. GABRIC:

Q. So I want to focus on Section 2.5.

A. Yes.

MR. GABRIC: Strike that. We're going to move on. We're going to move on. We're going to save ourselves the headache.

MR. PERLMAN: Do you want to withdraw the exhibit, or no?

MR. GABRIC: Yeah. I'm happy to withdraw the exhibit. It's already in the record.

THE WITNESS: Do you want the paper back?

MS. LYDIGSEN: Yes.

BY MR. GABRIC:

Q. Now, at Column 6, starting at Line 24, "The '974 patent reports pretreatment with a suitable amount of FBP binding agent from about one to about 24 hours is usually sufficient to substantively bind to and block the folate-binding protein prior to administration of the GARFT inhibitor or other antifolate."

Do you see that?

A. No. What paragraph?

Q. Column 6.

A. Yeah.

Q. Starting at Line 24.

A. Oh, 24. Okay.

Q. "The '974 patent reports pretreatment with suitable amount of FBP binding agent" --

A. Yes.

Q. -- "from about one to about 24 hours is usually sufficient."

Do you see that?

A. Yes, I do.

Q. Okay. And then it goes on to say, "Although one single dose of FBP binding agent, preferably oral administration of folic acid, should be sufficient to load the folate-binding protein, multiple dosing of the FBP binding agent can be employed for periods of -- for periods up to weeks before treatment with the active agent to ensure that the folate-binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment."

Do you see that?

A. I do.

Q. So this section is basically suggesting to one of ordinary skill in the art as of June of 1999 that you can pretreat with folic acid?

A. 1999? It was a 1991 patent.

Q. Yeah. As of 1999, one reading this patent would understand it to be saying you can pretreat with folic acid?

A. But a lot of things happened between 1991 and 1999. Right? You've given me the

papers --

Q. So are you saying one of ordinary skill in the art would ignore this teaching?

A. No. A person would know there were subsequent experiments that were done that showed that it quite effectively blocked lometrexol, both in terms of its toxicity and antitumor activity. But for pemetrexed, it didn't show the same efficacy.

Q. For the reasons you cite --

A. That we talked about.

Q. -- in your declaration?

A. Yes. Yes. So you asked me as of 1999. And a person's opinion as of 1999 would be what I said. I think as of 1991, this is -- there was no evidence for or against this in people. So...

Q. So I just want to understand your opinion. So your opinion is one of ordinary skill in the art, by the time they got to June of 1999, would not consider these teachings regarding folic acid?

A. Well, they would look at the patent and say: Did it work? And they would look at the lometrexol studies by Laohavinij, our friend, and say, geez, you know, he escalated and escalated.

He certainly affected toxicity. But he didn't get antitumor activity. And he stopped.

Q. That's the -- that's lometrexol we talked about earlier today --

A. Yes.

Q. -- that Lilly replaced in favor of a more active --

MR. GROSSMAN: Objection to the form of the question.

A. Well, not a more active compound. Another compound. It turned out not to be more active.

MR. PERLMAN: I ask you at 4:35, do you really have to do the whole thing all over again? At this point, you've spent --

MR. GABRIC: I appreciate the help. I don't know what I'd do without him.

MR. PERLMAN: I get antsy.

THE WITNESS: All right.

BY MR. GABRIC:

Q. So the '209 patent, if you can pull that out. Well, let me -- let me ask you a few questions.

In evaluating a therapeutic benefit of a chemotherapy regime, you can look at several

things, I take it? For example, are you reducing tumor size?

A. Right.

Q. And so a therapeutic benefit would cover reducing tumor size. Correct?

A. Right.

Q. Correct?

A. That's one -- one way of measuring it. There are other ways. One is -- the other is are you improving survival.

Q. Right. And preventing progression of the tumor is another way to evaluate whether you're receiving a therapeutic benefit. Correct?

A. That's been more recent. I think in the last 15 years, we have begun using that as a yardstick in a different sort of treatment environment with the targeted drugs.

Q. And in the June 1999 time frame, would one of ordinary skill in the art consider an improvement in therapeutic index to be a therapeutic benefit?

MR. GROSSMAN: Objection to the form of the question.

A. I think you have to define "therapeutic index" for me.

Q. You've heard that term before. Right?

A. Yeah. But I don't know what you think of it.

Q. Okay. How would you use -- how would one of ordinary skill in the art in June of 1999 use the term "therapeutic index"?

A. The idea would be that you get -- improving therapeutic index would be changing a regimen so that you get greater tumor responses and a longer survival without increasing the toxicity.

Q. And would one of ordinary skill in the art -- strike that.

COURT REPORTER: Steve.

THE VIDEOGRAPHER: Yes? Oh, I'm sorry.

MR. GABRIC: Yeah. Will you fix that?

THE VIDEOGRAPHER: We'll go off the record for just a minute at 4:38.

(A recess was taken.)

THE VIDEOGRAPHER: The time is 4:47. We're back on the record.

BY MR. GABRIC:

Q. Doctor, I want to put us in the pre-June 1999 time frame. Okay? And are you aware of physicians, when they're starting a

patient on an antifolate like methotrexate, that they -- they delay the initiation of treatment to accommodate the person's personal schedules? For example, they have a wedding coming up in a few days or they're taking trip. We'll start when you get back in a week?

A. Well, I think it depends on the tumor. If they've got leukemia, I don't think they'd be doing that. If it's something where you don't need an immediate response, you might delay for certain reasons.

Q. Okay. And one of ordinary skill would understand that, in June of 1999, that you could delay the onset of treatment depending on the type of tumor?

A. The circumstances. Yes.

Q. And what kind of delays would we typically see in that type of situation? Are we talking days, weeks, months?

A. Weeks.

Q. Weeks?

A. Maybe weeks. It depends totally on the circumstance. For example, with breast cancer adjuvant therapy, we know that if you delay beyond two months, you begin to have a higher

recurrence rate.

You know, with some patients with prostate cancer, which is a very slow-growing tumor, many patients, you may delay treatment for a year or two, just to observe the patient.

Q. And in what kind of tumors was methotrexate used?

A. Well, a large variety of tumors. So used for acute lymphocytic leukemia in children. It's used for choriocarcinoma in women. It tends to be a rapidly growing tumor. It's used for all sorts of lymphomas, in which many of them are very aggressive. It's used for intrathecal -- or intracranial lymphomas. It's the primary drug for intracranial lymphomas.

It's used in -- mostly outside of the United States for treatment of breast cancer, adjuvant treatment of breast cancer with a CMF regimen.

Q. And this was known in -- as of June of 1999?

A. Virtually all those were known, yes. I -- yes. They were known, almost without exception. There might have been -- one of the things on that list might have been after '99.

Q. Okay. I'm going to show you, Doctor,

what -- Lilly Exhibit 2091.

(Lilly Exhibit 2091 incorporated by reference.)

BY MR. GABRIC:

Q. And this is a document you cite in your declaration. It's the Wall Street Journal article from 2004?

A. Yes.

Q. And you were quoted in this article. Are you familiar with this article?

A. I am.

Q. All right. And I just have a few questions about it. How did it come to pass that you were being quoted in this article?

A. Because the Wall Street Journal called me out of the blue. I had no idea that they would call. You know, I'm pretty well known. I've been interviewed a lot of times by New York papers. So they probably thought, well, here is a guy that must know something about it.

Q. And so -- okay, so this -- did they ever explain to you how they got your name or who directed them to you?

A. I never asked them. And you can see it was a very short interview.

Q. And so this was -- you didn't prepare for this call? It was out of the blue?

A. It was just -- it happened. You know, I wasn't expected to be called. You know, people know that I'm involved in antifolates, so it's not -- not something new.

Q. And did -- did they -- you understood that this was a call about the invention that's the subject of the '209 patent?

A. At the time I was asked, no. I had no idea what the patent was like. I was not a patent-oriented person.

No. I can tell you the basis of this, if you want to know why my comment came. I had worked on this issue of reversing folates -- antifolates with folic acid and methotrexate for many years. And I had seen, you know, it's a competitive relationship. The more folate, the less activity of the antifolate. So I thought the whole idea of doing this was not sound.

Q. Now, you talked about earlier today that Dr. Niyikiza was an acquaintance, but not a close personal friend?

A. No.

Q. Correct?

A. I did say that, and he wasn't a close personal friend. And, in fact, at this time, I didn't know Dr. Niyikiza hardly at all. I actually met him when I -- when he had left Lilly and gone to GSK, and he was an adviser to Chris Viehbacher at GSK. And I knew Chris. And they asked me to be part of their scientific advisory group. And he happened to be there. And that's the way I met him. And I got to know him there. I don't think I had ever met him prior to the GSK experience, although I knew about the studies.

Q. As we sit here today, you don't consider him to be a very close personal friend?

A. No, not really. No.

Q. Okay.

A. If I see him once in a while --

Q. You gave a deposition in --

A. Yeah.

Q. -- the Lilly case?

A. Yeah.

Q. I just want to point you to some testimony in that case.

A. Okay.

(Sandoz Exhibit 1073 incorporated by reference.)

Q. And that's Exhibit -- could you tell me what we marked it with? Exhibit 1073? Is that correct? On the lower, right-hand column?

A. So where do I go?

Q. Why don't you go to Page 192.

A. Right.

Q. And this is a deposition that you gave --

A. Yeah.

Q. -- in that litigation. And the date was Tuesday, April 23, 2013. And you go to Page 192 --

A. I said I knew him when he was at Lilly, but I didn't know him well.

MR. PERLMAN: Doctor, Doctor, let him ask the question.

THE WITNESS: I'm sorry.

MR. PERLMAN: Then you give your answer.

MR. GABRIC: Thank you, Counsel.

Q. On Page 192 you were asked the question:

"QUESTION: How do you know Dr. Niyikiza?

"ANSWER: I've known him a long time. I knew him -- when he was at Lilly, I had met him.

And then I got to know him very well when he was Glaxo, and now he lives in Boston. He works for Merrimack. He's a very close personal friend. I see him for dinner often and we have a lot of things in common, believe it or not. He's a very, very smart man. He's a wonderful guy."

Did you give that testimony --

A. I did.

Q. -- in April of 2013?

A. Yeah. I used to see him frequently when he was at Merrimack. I haven't since he left. So I see him maybe once or twice a year, since that time. And I wouldn't consider him now a close personal friend.

Q. But you did in 2013?

A. Yeah. I think because he was working in Merrimack and I did see him a lot then when he was there. I also saw him when he was at GSK. And I don't know, you know, whether I knew him at Lilly or not. I mean, I knew of him. I knew who he was, but I don't know if I had met him. Maybe I had met him. But he certainly wasn't a close friend at that time.

Q. Now, in Paragraph 23 of your declaration --

A. Paragraph 23. Yes.

Q. Let me know when you're there. It's on Page 8.

A. Yes.

Q. And you set out your opinion on the person of ordinary skill in the art and the qualifications that person would have.

A. Yes.

Q. And I suspect you agree with that definition. That's your opinion. Right?

A. That's in here?

Q. Right.

A. Yes.

Q. Okay. Now, what about you personally? Are you one of ordinary skill in the art or are you one of exceptional skill in the art?

A. I think a person of ordinary skill in the art as defined legally would include anybody that knows everything I know.

Q. So you're one of ordinary skill in the art, not one of exceptional skill in the art?

MR. GROSSMAN: Objection to the form of the question.

A. I don't know what exceptional skill in the art -- is that a legal term? If it is, tell

me what it is, and I'll tell you whether I'm that.

Q. Well, I'm simply asking you if you have a view one way or the other. You've defined the person of ordinary skill here in Paragraph 23. Right?

A. Yeah, I think it's a person that is a medical oncologist that knows what is in the public domain and relevant to that field.

Q. Okay. And so my question is -- and this is a hypothetical person. You understand. Right?

A. I understand that.

Q. It's a hypothetical construct.

A. Right.

Q. And this hypothetical person only knows what is in the public domain in the prior art. Right?

A. Right.

Q. And you -- you know things that weren't in the public domain. Correct?

MR. GROSSMAN: Objection to the form of the question.

A. Do I know things that are not in the public domain? I know a lot of things that are

not in the public domain, yeah. But relevant to this case, I'm not sure I know much that's not in the public domain.

(Discussion off the record.)

Q. So your CV lists quite a few honors. Correct?

A. Right.

Q. And you've published 200-plus peer-reviewed articles and books. Right?

A. Yes.

Q. The person of ordinary skill in the art, do they need to have done that to qualify as one of ordinary skill in the art?

MR. GROSSMAN: Objection to the form of the question.

A. I think it should be a person who is knowledgeable about everything that's in the public domain. Yes. And so they've read my papers and they would know -- know what I've done.

Q. Does a person of ordinary skill in the art have to have published papers to qualify?

A. I don't think that that's a necessary attribute, although I would think that if a person is that well-read and that knowledgeable

that they will have done research.

Q. Well, in your opinion, does a person of ordinary skill in the art, as you define it, do they have to have published papers?

A. Do they have to have published papers? Well, it's pretty hard to find anybody that's that competent that hasn't published a paper. I would think that they would, yes.

Q. Is there any particular number of papers, 50, 100?

A. I haven't put a number on it, but I would expect they would have published.

Q. Let's say they published a hundred papers.

A. That's pretty good.

Q. You would consider them to be one of ordinary skill in the art, that's good enough?

A. I don't think that that's the only criterion, though. I think that there are people that publish a lot of junky papers that wouldn't qualify. I can give you some good examples of that.

Q. Let me ask you this. Is one of ordinary skill in the art, would they have to have a CV like your CV to qualify as one of

ordinary skill in the art?

A. No.

Q. They could be less accomplished than you?

A. I wouldn't say less accomplished. They might have published less papers. There are people with Nobel Prizes that have published 30 papers. It depends how important the work is.

(Discussion off the record.)

MR. GABRIC: Why don't we take a two-minute break. I'll consult with my colleagues.

MR. GROSSMAN: Sure.

THE VIDEOGRAPHER: The time is 5 o'clock, and we're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: The time is 5:08, and we're back on the record.

BY MR. GABRIC:

Q. Let us know when you're ready, Doctor.

A. I'm sorry.

Q. It's okay.

A. It's something important.

Q. No worries.

A. Okay.

Q. I just have one last thing. And we briefly touched on it. You mentioned earlier today that your first contact with Lilly was on a project.

A. Forteo project.

Q. Yeah. When did -- when did that start?

A. It started something around 2001 or 2002. It was with the endocrine division.

Q. And have you been involved in any other projects with Lilly since then, other than that project and this litigation?

A. You know, I don't remember any projects I've been involved with with them. No. I'm not on their scientific advisory board. We've actually not done many clinical trials with them at the MGH. I do know Rich Gaynor there, but he's now gone, and he was the head of oncology. And I've known him just through charitable activities, not through formal work there.

Q. Have you or any of the organizations that you work with received honorariums, financial honorariums from Lilly over the years?

A. You know, I might have at one time. 1996, I think it was, I was asked to be the visiting professor at the Indiana University.

And it was called the Eli Lilly Lectureship. I actually showed a picture there of my two dogs in bed with me. And their names were Eli and Lilly. And I said, you know, I've been accused of being in bed with Eli Lilly. It was a joke. And I am. And that is the closest I've been to being in bed with Eli Lilly, yes. They've tended to work with the Dana Farber more than Mass. General.

Q. So the -- so we have this professor chairship, I don't know if that's the right term. But anything else besides this Indiana U?

A. You know, I don't remember anything else. There could have been some other thing, but nothing that I can recall. I mean, if you -- maybe you could refresh my memory, but...

Q. Just curious, why did you name your dogs Eli and Lilly?

A. Because I went to Yale. And then what do you do when you have Eli? You've got to find a woman's name, so it was Lilly.

Q. Got it.

A. It had nothing to do with the drug company.

MR. GABRIC: Thank you, Doctor, for your time. I know it's been a long day. I pass

the witness.

THE WITNESS: Good. Okay.

MR. PERLMAN: We'll go off the record.

THE VIDEOGRAPHER: The time is 5:11. We're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: The time is 6:05. And we're on the record.

REDIRECT EXAMINATION

BY MR. GROSSMAN:

Q. Good afternoon, Dr. Chabner.

A. Good evening.

Q. Good evening. Dr. Chabner, you have in front of you Exhibit 1063. You were asked a number of questions about that earlier.

In the cancer context, are Phase 1 trials typically conducted in cancer patients or healthy volunteers?

A. Cancer patients.

Q. And outside the cancer context, are Phase 1 trials typically conducted in patients suffering from a disease or healthy volunteers?

A. Normal volunteers, usually.

Q. And Exhibit 1063, is that specific to

the cancer context, or does that refer to clinical trials, Phase 1 trials?

A. It's clinicaltrials.gov, from NIH. So it's the whole thing. All of NIH.

Q. So is 1063 specific to the cancer context?

A. No.

Q. Dr. Chabner, you were also asked a number of questions about the two Hammond references. And I believe you have those two in front of you. Exhibits 1014 --

A. Yeah.

Q. -- and 1015.

Do the Hammond references provide information about the folic acid pretreatment regimen that the patients received?

A. Yes.

Q. And what was that regimen?

A. It's 5 milligrams beginning two days before and continuing for three days after treatment.

Q. And would the person of ordinary skill have an understanding as to whether all the patients in Hammond received the same folic acid pretreatment regimen?

A. Yes.

Q. And what would that understanding be?

A. They did.

Q. You were also asked some questions, Dr. Chabner, about lometrexol and why Lilly discontinued development of lometrexol. And you also were asked some questions about the Laohavinij reference, Exhibit 2031?

A. Yes.

Q. Would the Laohavinij reference factor into the person of ordinary skill's understanding as to why development of lometrexol was discontinued?

A. Yes.

MR. GABRIC: Objection. Leading.

Q. How so?

A. Because the regimen was ineffective --

Q. And --

A. -- as an anticancer regimen.

Q. And why it was ineffective as an anticancer regimen?

A. One response.

Q. And that was with folic acid pretreatment?

A. Yes.

Q. And how did the regimen appear without folic acid pretreatment?

A. It was toxic.

Q. Now, if you could turn to -- I believe you have in front of you Exhibit 1013, which is the Worzalla anticancer article. And I'd like you to turn to Page 3237, and the top is Table 1. Do you see that?

A. Yes.

Q. Do you recall being asked some questions about that by --

A. Yes.

Q. -- counsel earlier? Now, and one of the -- the left-hand column is looking at the effect of the change in IC50 of folic acid?

A. Correct.

Q. And the left -- sorry, the right-hand is looking at folinic acid. Do you see that?

A. Got it.

Q. If a person were to receive folic acid pretreatment, which of these columns, folic acid or folinic acid, would better reflect the state of the folate in the body by the time they received the antifolate?

A. It would be rapidly -- the folic acid

would be rapidly converted to 5-methyltetrahydrofolate and go through that pathway to tetrahydrofolate, which is then the precursor of all the necessary folate cofactors for the making of DNA.

Q. And so --

A. So essentially it's converted to folinic -- like folinic acid to tetrahydrofolate.

Q. So would the person of ordinary skill regard the folinic acid here as more relevant to the effect of folic treatment -- folic acid pretreatment?

A. Folic acid and to folinic. In terms -- this is a cell culture experiment, so you don't get that transition, but in people, folic acid would be converted rapidly to a tetrahydrofolate.

Q. And tetrahydrofolates reduce folate?

A. Yes, it is.

Q. Folic acids reduce folate?

A. Yes. Folinic acids reduce folate.

Q. You were asked some questions, Dr. Chabner, about Exhibit 1067, which are these charts prepared -- or demonstratives prepared by Dr. Ratain for the Indianapolis trial. Do you

recall that?

A. Yes.

Q. I'd like you to take a look at Slide 72.

A. Right.

Q. Now, what does this slide teach the person of ordinary skill in terms of whether or not there is a therapeutic window for the mice on the low-folate diet?

A. There is.

Q. And what does it teach the person of ordinary skill about whether there is a therapeutic window for the mice on the standard diet?

A. There is one also there.

Q. And to the extent there is a difference here between the data for the standard diet and the mice on the low-folate diet with folic acid --

A. Supplementation.

Q. -- with folic acid supplementation, how would the person of ordinary skill regard any such difference with respect to the use of folic acid pretreatment in humans?

A. I don't think the difference really is

significant, because you never get beyond this point in the curve. I don't think you even get close to it in terms of the human tolerance for the doses that were being used here. And so I don't think the point is -- you know, this difference is important.

Q. And that's -- and you're talking about -- when you say the --

A. The therapeutic window that says that supposedly there's no toxicity up to a thousand in the supplemented diet. But I don't think you'd ever get there with -- even close to that in a human because of the massive doses of pemetrexed that are being used. So --

Q. What would the person of ordinary skill expect if you used such massive doses in humans?

A. I think you'd have renal failure, first of all.

Q. Now, Dr. Chabner, you were also asked a number of questions about the conclusions in Exhibit 1013, that Worzalla article that you just looked at.

A. This one (indicating)? Yeah.

Q. As well as Exhibit 1068, which contains the Worzalla abstract.

A. Abstract. Right.

Q. And you were asked about the relevance of those conclusions to the use -- potential use of folic acid pretreatment in humans. Do you recall that?

A. Yes, I do.

Q. As of June 1999, was there additional information in the prior art about folic acid pretreatment with pemetrexed in humans?

A. Yes, there was.

Q. And what information was that?

A. The Hammond trials showed that you've got a very different kind of response rate in the Phase 1 trial. One response versus the ten responses you saw with Rinaldi in the unsupplemented trial. So it didn't look like a promising direction to go in.

Q. Now, Dr. Chabner, you were asked some questions from counsel about the Arsenyan article. Do you recall that?

A. Yes.

Q. And you were asked some questions suggesting about whether or not you had ever cited Arsenyan in any of your papers?

A. Yes.

Q. Did any of your colleagues -- are you aware of whether any of your colleagues cited the Arsenyan reference?

A. Yes. Lionel Poirier did. On the Linlal -- Lillin paper. I can't remember the first author's name. It begins with L. But it was a paper showing stimulation with cobalamin, and he quoted Arsenyan.

Q. And who was Lionel Poierier?

A. He was a colleague at NCI. I knew him when I was there.

MR. GROSSMAN: Can we mark this as Exhibit 2140.

(Article entitled "Tissue Distribution of Methylcobalamin in Rats Fed Amino Acid-Defined, Methyl-Deficient Diets" marked Exhibit 2140.)

BY MR. GROSSMAN:

Q. Dr. Chabner --

A. Linnell. Right.

Q. -- is that the article you're referring to?

A. Yes.

Q. And take a look at Footnote 1.

A. Reference 1?

Q. Reference 1.

A. Yeah.

Q. What reference is that?

A. It's the Arsenyan.

Q. It's the reference we were discussing earlier?

A. Yes.

Q. And for what purpose does Exhibit 2140, the Linnell article cite Arsenyan?

A. It validates the statement, cobalamin stimulates the replication of many cell types during in vivo -- both in vivo and in vitro. That's one of five references.

Q. Now, Dr. Chabner, you were also asked some questions about the studies in the Arsenyan reference and in the Sophyna reference that involved methylcobalamin. Do you recall that?

A. Yes.

Q. If the person of ordinary skill were to perform those experiments with cyanocobalamin instead of methylcobalamin, would the person of ordinary skill expect the results to be similar to those obtained with methylcobalamin?

A. Cyanocobalamin is essentially very similar, if not the same thing, as giving

methylcobalamin -- or exposing methylcobalamin in vitro. Because in the body, when you take cyanocobalamin, it's converted to methylcobalamin. It's just a convenient way of giving B12.

Q. And so based on that understanding, what would the person of ordinary skill expect if the experiments in Sofyina and Arsenyan involving methylcobalamin were repeated with cyanocobalamin instead?

A. I think the results would have been the same in the in vivo experiments. In the in vitro experiments, I'm not sure that you get the conversion. But when you give it to an animal, it happens.

Q. Now, Dr. Chabner, earlier you were asked some question about the methyl trap. Do you recall that?

A. I do.

Q. Is the phrase "methyl trap" something that you made up for purposes of this case?

A. No. It was -- I think it was first offered by Victor Herbert, who was an expert in folate and B12 metabolism.

Q. Would the person of ordinary skill,

whether referred to as the methyl trap or the substance of what it's talking about, but would the person of ordinary skill understand that such a phenomenon exists in June of 1999?

A. Yes. He was a very well-known person in the field. His papers were. But I'm not sure he was the first. There may have been somebody before him. But he certainly was involved in that.

Q. Would the person of ordinary skill understand that there was such a phenomenon that if there weren't sufficient levels of cobalamin, that tetrahydrofolate could get trapped in a methyl trap as 5-methyltetrahydrofolate?

A. Yes. I think that was well known.

Q. You were also asked some questions, Dr. Chabner, about the Rinaldi reference, Exhibit 2030. Do you recall that?

A. Yes.

Q. And you were asked a number of questions. If you turn to Page 84 of the reference.

A. Yes.

Q. You were asked a number of questions about that weekly times four dosaging regimen.

A. Right.

Q. Was that the dosaging regimen that was selected for Phase 2 clinical trials?

A. No.

Q. What was the regimen that was selected for Phase 2?

A. It was an every-three-week bolus dose.

Q. And is that the dose that was in the Hammond abstracts that we saw?

A. That's right.

Q. And was that the dose that was in the Rusthoven paper that we looked at?

A. Yes.

Q. Okay. Now, Dr. Chabner, you were also asked questions about Exhibit 1070.

A. 1070. Where is that?

MR. GROSSMAN: Here you go.

THE WITNESS: Okay.

Q. Which is an abstract by Paz-Ares. Do you see?

A. I do.

Q. And what types of patients were the subject of this study that's reported here in abstract 1307?

A. So there were 22 patients with advanced

transitional cell carcinoma of the bladder.

Q. And what would the person -- would the person of ordinary skill have any understanding about how that patient population differed from other patient populations that could affect the toxicity observed in the study?

A. Well, I believe I mentioned that, that these patients -- many of the patients have altered renal function due to obstruction of the ureters. They've -- many of them have been prior -- have received prior treatment to the pelvis with radiation therapy. And that would compromise their bone marrow function. And, thirdly, the primary regimens for this disease may include cisplatin, which is a renal toxin.

So I think all of those factors could make them significantly more sensitive to -- to a drug that depends on renal excretion.

Q. So would the information in this abstract affect the person of ordinary skill's understanding from other prior art that -- strike that.

Would the information in this abstract change the person of ordinary skill's understanding, as you expressed in your

declaration, as to whether pemetrexed, as of June 1999, had toxicities that were manageable and tolerable?

MR. GABRIC: Objection. Leading.

A. No.

MR. GABRIC: I'm sorry, Doctor. I just have to get my objection in. Objection. Leading. Go ahead.

THE WITNESS: Okay.

A. No. I think that the toxicity -- the descriptions of toxicity in the other major tumor types were -- were accurate, and they reflected that it was manageable and -- with usual dose adjustments and changes in schedule.

Q. Dr. Chabner, you were also asked some questions about Exhibit 1072, which is the Neupogen labeling.

A. Oh, right.

Q. And I'd like to direct your attention to Page 14 --

A. Right.

Q. -- under the "Precautions" section.

A. Mm-hmm. Yes.

Q. And what does -- and I'd also -- take a look, it says there, "Because of the potential

sensitivity of rapidly dividing myeloid cells to cytotoxin chemotherapy, do not use Neupogen in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy."

Do you see that?

A. I do.

Q. And on Page 23 of the reference --

A. Mm-hmm.

Q. -- second full paragraph under "Dosage and Administration" --

A. Yes.

Q. -- it says, "Neupogen should be administered no earlier than 24 hours after the administration of cytotoxin chemotherapy. Neupogen should not be administered in the period 24 hours before the administration of chemotherapy."

Do you see that?

A. Yes, I do.

Q. What relevance would the person of ordinary skill ascribe to those statements in terms of -- strike that.

Why would the person of ordinary skill understand that those directions were included in this document?

MR. GABRIC: Objection. Leading.

A. They were included because when you stimulate the marrow, as Neupogen does, into cell division, rapid cell division, it becomes very sensitive to injury by chemotherapy at that point.

Most chemotherapy is directed at cells that are undergoing active DNA synthesis. Same thing would apply to B12, folic acid, colony stimulating factor.

Q. And so how does the -- how do the instructions here comport with your opinions concerning whether or not to give folic acid and B12 pretreatment?

A. That's why the -- yeah. That's why the compendiums say don't give B12. And the same reservation applies to folic acid, which is -- which would stimulate tumor, would stimulate marrow. So it could injure the marrow --

Q. Dr. Chabner --

A. -- in a deficient patient.

Q. -- you were asked some questions about whether dose adjustments and schedule adjustments could affect the efficacy of pemetrexed. Do you recall that?

A. Yes.

Q. Okay. Why would the person of ordinary skill think that dose and schedule adjustments were viable approaches for dealing with toxicity, but that pretreatment with folic acid and Vitamin B12 would not be a viable strategy?

MR. GABRIC: Objection. Leading.

A. I'm not sure why they would think that. The dosing schedule adjustments are the standard for every chemotherapy that we use. And we manage to do it without risking the strategy of giving something that could stimulate tumor growth.

Q. And when you say -- when you say "without the strategy of stimulating tumor growth," what are you referring to?

A. Folic acid, B12.

Q. And so would the person of ordinary skill pursue a strategy of folic acid and Vitamin B12 pretreatment?

A. Not when they can do the other. At least that was my thinking at the time.

Q. And would that have been the person of ordinary skill's understanding as of June 1999?

A. Yes. It was well known. Yes.

MR. GROSSMAN: Thank you, Dr. Chabner. No further questions.

Oh, sorry, Doctor. I have one additional question. I apologize.

Can we mark these as 2041 and 2042 [sic].

(Transcript of trial proceedings dated August 26, 2013 marked Exhibit 2141.)

(Transcript of trial proceedings dated August 27, 2013 marked Exhibit 2142.)

BY MR. GROSSMAN:

Q. Dr. Chabner, you've been handed Exhibits 2041 and 2042. Do you recall being asked a number of questions earlier today about your cross testimony at the trial in Indiana in 2013?

A. I do.

MR. GABRIC: Counsel, let me just interject. I'm going to object to these exhibits. I don't believe these are properly admissible in evidence in the way you're trying to use them.

BY MR. GROSSMAN:

Q. Dr. Chabner, have you had a chance -- do you recall being asked those questions

about --

A. Yes, I do.

Q. Have you had a chance to look into whether -- and do you recall in the Indiana trial first there was a direct examination by myself, followed by a cross by Mr. Weisen?

A. Right.

Q. Followed by a redirect by myself?

A. Right.

Q. And have you had a chance to look through these documents?

A. I have.

Q. And does this reflect your complete trial testimony from the Indiana trial?

A. Yes.

MR. GROSSMAN: I have no further questions. Thank you, Dr. Chabner.

MR. GABRIC: Would you give us two minutes. We won't be long, Doctor. Don't panic. I'll be back sooner than 50 minutes.

THE VIDEOGRAPHER: Going off the record. 6:27.

(A recess was taken.)

THE VIDEOGRAPHER: The time is 6:32. We're back on the record.

MR. GABRIC: Thank you, Dr. Chabner. I have no questions. Don't look so disappointed.

THE VIDEOGRAPHER: This concludes the deposition of Bruce Chabner, M.D. The time is 6:32. And we are off the record.

(Deposition concluded at 6:32 p.m.)

C E R T I F I C A T E

COMMONWEALTH OF MASSACHUSETTS

SUFFOLK, SS.

I, Janet M. Sambataro, a Registered Merit Reporter and a Notary Public within and for the Commonwealth of Massachusetts do hereby certify:

THAT BRUCE A. CHABNER, M.D., the witness whose testimony is hereinbefore set forth, was duly sworn by me and that such testimony is a true and accurate record of my stenotype notes taken in the foregoing matter, to the best of my knowledge, skill and ability; that review was not requested.

I further certify that I am not related to any 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 11th day of November, 2016.

_____

JANET M. SAMBATARO

Notary Public

My Commission Expires:

July 16, 2021

ERRATA SHEET:

Case Name: Sandoz vs. Eli Lilly
Dep. Date: 11/10/16
Deponent: Bruce Chabner, M.d. Bruce Chabner, M.D

CORRECTIONS:

Pg.	Ln.	From	To	Reason
315	18	tetrahydrofolates reduce folate	tetrahydrofolate is a reduced folate	transcription error
315	20	folic acids reduce folate	folinic acid is a reduced folate	transcription error
315	21	folinic acids reduce folate	Folinic acid is a reduced folate	transcription error
320	16	Sophyna	Sofyina	typographical error

Subscribed and sworn to before

me this 12th day of December, 2016.

Jean Tammaro

JEAN TAMMARO
Notary Public
Massachusetts
Commission Expires Mar 9, 2018