

In the Matter Of:
CSPC Pharma vs Ipsen Biopharm

IPR2025-00505

MARK J. RATAIN M.D.

October 24, 2025

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1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD
4

5
6 CSPC PHARMACEUTICAL GROUP LIMITED,
7 CSPC OUYI PHARMACEUTICAL CO., LTD., AND
8 CONJUPRO BIOTHERAPEUTICS, INC.,

9 Petitioners,

10 v.

11 IPSEN BIOPHARM LTD,

12 Patent Owner.
13

14 Case No. IPR2025-00505

15 Patent No. 11,344,552
16

17 DEPOSITION OF MARK J. RATAIN, M.D.

18 Conducted via Zoom

19 Witness Location: Chicago, Illinois

20 Friday, October 24th, 2025
21

22 THIS DOCUMENT HAS BEEN DESIGNATED CONFIDENTIAL
23

24 REPORTED BY: GREG S. WEILAND, CSR, RDR, CRR

25 JOB NO.: J13642857



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October 24th, 2025
8:59 a.m. Central Daylight Time

Deposition of MARK J. RATAIN, M.D.,
conducted via Zoom, taken before GREG S. WEILAND,
CSR, RDR, CRR, pursuant to the Federal Rules of
Civil Procedure for the United States Patent and
Trademark Office pertaining to the taking of
depositions, commencing at 8:59 o'clock a.m. Central
Daylight Time, on the 24th day of October, 2025.



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1 PRESENT:

2
3 ON BEHALF OF THE PETITIONERS:

4 FOX ROTHSCHILD LLP

5 BY: MR. HOWARD S. SUH (via Zoom)

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10 - and -

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1 PRESENT (CONTINUED):

2
3 ON BEHALF OF THE PATENT OWNER:

4 QUINN EMANUEL URQUHART & SULLIVAN, LLP

5 BY: MS. CATHERINE T. MATTES (via Zoom)

6 MR. ANGUS CHEN, Ph.D. (via Zoom)

7 MS. ELIZABETH J. MURPHY (via Zoom)

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16
17 ALSO PRESENT:

18 MS. JUDITH KUNTZ (via Zoom)

19 MR. THOMAS J. PAXTON (via Zoom)

20 MS. KAREN MARTIN (via Zoom)

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15		locally advanced or metastatic	
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17		junction adenocarcinoma, Roy,	
18		et al.	
19	Exhibit 1200	Supplemental Expert Declaration	14
20		of Mark J. Ratain, M.D.	
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22			
23	REPORTER'S NOTE: All quotations from exhibits are		
24	reflected in the manner in which they were read in		
25	the record and do not necessarily reflect exact		
	quotes from the source documents nor necessarily		
	match the punctuation.		

1 (Witness sworn.)

2 MS. MATTES: Good morning, Dr. Ratain. As
3 I said before, my name is Catherine Mattes.
4 I'm here today representing my client,
5 Ipsen Biopharma, and we're here for an
6 inter partes review proceeding for
7 United States Patent Number 11,344,552.

8 So thank you for joining today.

9 MR. SUH: I'm sorry. Ms. Mattes, I just
10 wanted to make sure. Are we going to be doing
11 appearances with the attorneys?

12 MS. MATTES: Sure. If you would like to,
13 you can.

14 With me here today who are participating,
15 who are also on the Zoom with me, are my
16 colleagues Angus Chen, Elizabeth Murphy, and
17 Ross Misskelley.

18 MR. SUH: Okay. So my name is Howard Suh
19 from the law firm of Fox Rothschild
20 representing petitioner.

21 With me is my colleague Dr. Joe Chen, also
22 with Fox Rothschild.

23 MS. MATTES: Okay, great. Thank you very
24 much.

25



1 MARK J. RATAIN, M.D.
2 after being first duly sworn, testified as follows:
3 EXAMINATION
4 BY MS. MATTES:
5 Q. Dr. Ratain, you're appearing today via
6 Zoom in Chicago; is that correct?
7 A. Yes.
8 Q. And besides the two attorneys sitting, I
9 guess, to your right, is anybody else in the room
10 with you?
11 A. Just the two attorneys.
12 Q. And can you confirm that you can hear me
13 and see me okay?
14 A. I can. You know, occasionally, it
15 reverberates a little bit, but I think it will be
16 okay. And if I don't hear you, I'll ask you to
17 repeat it.
18 Q. Okay, great. Sometimes I speak quickly,
19 so if you -- if it's coming across too quickly, let
20 me know, and I'll try to slow down. And if my voice
21 ever drops, please also let me know.
22 Do you have -- do you have any documents,
23 notes, or other electronic devices with you other
24 than what's visible on camera?
25 A. Just my phone.



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1 Q. Okay. And besides the Zoom screen, are
2 you looking at any other screens or laptops?

3 A. No.

4 Q. And do you understand that you should not
5 be communicating with anybody else during the
6 deposition, except for when you are on a break?

7 A. I do.

8 Q. And if we need to display -- this
9 shouldn't be the case, but if we need to display
10 documents, you understand how screen sharing works?

11 A. I do, but I probably would prefer to see
12 hard copies. So if you do --

13 Q. Okay.

14 A. -- think you want to do something, I would
15 ask that you email it to the office here so that it
16 could be printed for me.

17 Q. Okay. That's fine. I think that's a fair
18 request.

19 And so I see on the desk there's a box of
20 documents. If -- I would like to represent that
21 those are the documents that are the exhibits that
22 came along with your expert declarations, minus a
23 few. Some of the larger file history documents are
24 not included in there.

25 So if we're having -- during the course of



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1 the deposition, if you feel the need to look at a
2 specific document that, let's say, I haven't yet put
3 in front of you or asked you to look at, you can
4 know that you have that box available to you. It
5 should have the majority of the exhibits that came
6 along with your declaration.

7 Okay?

8 A. Thank you.

9 Q. So, Dr. Ratain, have you been deposed
10 before?

11 A. Yes.

12 Q. Approximately how many times have you been
13 deposed?

14 A. I don't -- I can't give you a good number.

15 Q. Is it more than ten?

16 A. Yes.

17 Q. More than 50?

18 A. Maybe.

19 Q. Okay. And have most of those depositions
20 been in your capacity as an expert witness?

21 A. Not all of them. I've been a fact witness
22 maybe a couple times.

23 Q. Okay. And do you understand that you are
24 under oath today and that your testimony has the
25 same force and effect as it's given in open court?



1 A. I do.

2 Q. And if you do not understand one of my
3 questions today, will you please let me know?

4 A. Yes.

5 Q. And do you understand that if you answer a
6 question, I will assume that you understood the
7 question?

8 A. Yes.

9 Q. And if you need to take a break at any
10 time, please let me know. However, if there's a
11 pending question, I'll just ask that you answer it
12 before we take a break.

13 Is that acceptable?

14 A. Yes.

15 Q. Is there any reason why you cannot give
16 truthful and accurate testimony today?

17 A. No.

18 Q. And have you had an opportunity to review
19 any documents or materials in order to prepare for
20 today's deposition?

21 A. Yes.

22 Q. And would that include your two expert
23 declarations that you submitted as part of this
24 proceeding?

25 A. Yes.



1 Q. Have you ever had your -- I guess I asked
2 you if you've been deposed before.

3 But have you ever -- have you ever
4 testified in court?

5 A. Yes.

6 Q. Have you ever had your testimony excluded
7 or limited by a court in any way?

8 A. Some of my testimony has been excluded
9 because it was deemed -- because part of the report
10 itself was deemed nonresponsive to -- it was, I
11 think, a surreply report. And counsel had to, you
12 know, deal with the fact that some of the material
13 was deemed to be nonresponsive and, therefore, was
14 stricken from the report and, therefore, stricken
15 from the live testimony.

16 Q. Okay. Understood. Have you ever been
17 disqualified as an expert in any proceeding?

18 A. No.

19 Q. No, okay. So you understand, obviously,
20 that you've been retained as an expert witness for
21 purposes of this proceeding today?

22 A. Yes.

23 Q. And who retained you as an expert in this
24 matter?

25 A. Fox Rothschild.



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1 Q. And you understand that you're being
2 deposited today in your capacity as an expert witness?

3 A. Yes.

4 Q. And you've provided two written reports
5 for purposes of this proceeding, correct?

6 A. Well, declarations.

7 Q. I'll rephrase.

8 So you've provided two declarations in
9 this case, correct?

10 A. Yes.

11 (Exhibit 1002 and Exhibit 1200
12 were marked for identification.)

13 BY MS. MATTES:

14 Q. And so we've premarked those as
15 Exhibits 1002 and Exhibit 1200.

16 So I would request that maybe your
17 attorneys place those before you so you have them
18 nearby because they're documents that we will be
19 referencing quite often today.

20 The folders should be labeled with the
21 exhibit numbers. Please let me know if anything is
22 not there.

23 So, Dr. Ratain, do you have Exhibit 1002
24 in front of you?

25 A. Yes.



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1 Q. And can you please just take a look
2 through it and let me know, is this your declaration
3 that's dated January 17th, 2025?

4 A. It appears to be. I haven't checked every
5 page, but assuming that there's no missing pages, it
6 is.

7 Q. Okay. And this is the first declaration
8 you submitted in this proceeding, correct?

9 A. Yes.

10 Q. And if you go to Page 126 of your expert
11 report, that's your signature on that page, correct?

12 A. Yes.

13 Q. And did you review this declaration before
14 you signed it?

15 A. I did.

16 Q. And was this declaration true and accurate
17 at the time you signed it?

18 A. Yes.

19 Q. And is it still true and accurate today?

20 A. I don't recall whether there's anything in
21 here that might relate to specific number of
22 publications or something for that matter, but I
23 believe it's -- nothing has changed substantially.

24 I obviously have more publications. My
25 curriculum vitae is not the same vitae, so ...



1 Q. So outside of your curriculum vitae, in
2 terms of the substance of the opinions that you're
3 offering in this report, everything is still true
4 and accurate today?

5 A. Yes.

6 Q. Is there anything that you would -- let me
7 start over again.

8 In preparation for today's deposition, did
9 you review this expert declaration?

10 A. I read it, yes.

11 Q. Are there any changes or modifications
12 that come to mind or came to mind upon reviewing the
13 declaration for purposes of your deposition today?

14 A. No.

15 Q. Okay. So do you also have Exhibit 1200 in
16 front of you?

17 A. Yes.

18 Q. And is this the second declaration that
19 you submitted in this case?

20 A. It is.

21 Q. And it's dated June 22nd, 2025?

22 A. Yes.

23 Q. And is that your signature on the last
24 page of the declaration? I believe it's Page 6.

25 A. It is.



1 Q. Did you review this declaration before
2 signing it?

3 A. Yes.

4 Q. And was this second declaration true and
5 accurate when you signed it?

6 A. It was.

7 Q. And is it still true and accurate today?

8 A. Well, yes. I mean, there's -- there's
9 even additional evidence that would support that,
10 just as I -- based on the material in your brief, I
11 looked at two other documents in response to a
12 couple of the things that were submitted as part of
13 the -- either the discretionary denial brief or the
14 preliminary response brief.

15 Q. And that's what's contained in this second
16 declaration, your response to materials provided in
17 the discretionary denial brief?

18 A. No, it's just additional -- well, it's
19 additional materials related to "New Evidence
20 Further Rebuts Patent Owner's Unexpected Results
21 Arguments."

22 Q. Right. And that's the -- right.

23 And what you're referring to is what's
24 contained in your second expert declaration,
25 correct?

1 A. Yes.

2 Q. Okay. And since submitting these two
3 declarations, have any of your opinions changed?

4 A. No.

5 Q. Okay. Thank you.

6 Your opinions are focused on the validity
7 of United States Patent 11,344,552, correct?

8 MR. SUH: Objection to form.

9 THE WITNESS: Well, my opinions are
10 limited to the obviousness of the patent, the
11 opinions expressed in my declarations.

12 BY MS. MATTES:

13 Q. Okay. Fair enough.

14 And if I call the U.S. Patent 11,344,552
15 just the "'552 patent," that would be okay with you
16 for purposes of today?

17 A. Yes. You can even call it "the patent" to
18 save yourself some time.

19 Q. "The patent." Well, there are multiple
20 references that are patents, so I don't want to
21 confuse -- confuse the record. So I'll stick to the
22 "'552 patent."

23 Is that all right with you?

24 A. Sure.

25



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1 (Exhibit 1001 was marked for
2 identification.)

3 BY MS. MATTES:

4 Q. And if your attorneys wouldn't mind
5 presenting to you Exhibit 1001, which should be the
6 '552 patent.

7 A. I have that.

8 Q. Great. And is this the '552 patent that
9 is the focus of your opinions?

10 A. Well, again, it's got 82 pages, so I'm not
11 checking every page number, but it appears to be
12 every page of the patent.

13 Q. Okay. Dr. Ratain, what is your
14 understanding as to what the claimed invention of
15 the '552 patent is?

16 A. Well, the claimed invention of the '552
17 patent is a method of treating advanced pancreatic
18 cancer.

19 Q. And what is the -- what is the method that
20 is being claimed in this patent?

21 A. Well, the claims specifically relate to a
22 specific recipe to treat metastatic pancreatic
23 cancer, adenocarcinoma of the pancreas, in patients
24 who have not previously received any chemotherapy.

25 Q. And what is the recipe that is being

1 claimed?

2 A. The recipe that's being claimed is
3 administration of four drugs every two weeks. The
4 specific drugs are liposomal irinotecan,
5 oxaliplatin, leucovorin, and 5-fluorouracil.

6 And the claim 1, which is the only
7 independent claim -- I'm sorry, claim 1 and claim 12
8 are the two independent claims. They both have very
9 specific dosages for the four drugs.

10 Q. Okay. And are those dosages also -- those
11 are listed in the claims you just cited, correct?

12 A. Yes.

13 Q. Okay. And that's 60 milligrams per meter
14 squared of liposomal irinotecan, correct?

15 A. Yes.

16 Q. And then 60 milligrams per meter squared
17 of oxaliplatin?

18 A. Yes.

19 Q. And 200 milligrams per meter squared of
20 leucovorin? Or, I guess, 400 milligrams per meter
21 squared of leucovorin, depending on the racemic --
22 whether it's an enantiomer or the racemic form; is
23 that right?

24 A. Yes.

25 Q. And then 2400 milligram per meter squared

1 of 5-fluorouracil, correct?

2 A. Yes.

3 Q. And is it your understanding that these
4 are the starting doses of the claimed treatment?

5 A. They're the only doses of the claimed
6 treatment.

7 Q. And so a person of skill in the art
8 looking at this method would perform it by
9 administering to patients starting doses of
10 60 milligrams per meter squared of liposomal
11 irinotecan, correct?

12 MR. SUH: Object to form.

13 THE WITNESS: To practice this claim, you
14 would administer these doses every two weeks
15 without delay or dosage reduction.

16 BY MS. MATTES:

17 Q. Correct. And so when patients would be
18 starting on this regimen, these would be the doses
19 that they would receive, correct?

20 A. Yes, and then every two weeks thereafter.

21 Q. Okay. Understood.

22 Okay. You can put this patent to the
23 side. Thank you.

24 Now, if you take out Exhibit 1002, which
25 is your first expert declaration, and can you please

1 go to Paragraph 25.

2 A. I'm sorry. What's the paragraph number?

3 Q. 25.

4 A. 25?

5 Q. Correct. So here you write that you've
6 been asked to consider whether claims 1 and 3
7 through 15, "the challenged claims," of the '552
8 patent are obvious in view of the prior art.

9 Do you see that?

10 A. That's -- that is what Paragraph 25 says,
11 yes.

12 Q. Okay. So I just want to confirm that you
13 were not asked to consider whether claim 2 of the
14 '552 patent is obvious in view of the prior art,
15 correct?

16 A. That's correct.

17 Q. And so you're not offering any opinions
18 with respect to whether claim 2 of the '552 patent
19 is obvious?

20 A. I am not.

21 Q. When you were asked to consider whether
22 the challenged claims of the '552 patent were
23 obvious, how did you go about -- what process did
24 you use?

25 MR. SUH: Object to form.



1 THE WITNESS: Well, I -- I began by
2 looking at what the priority date was for the
3 patent application, and I considered what a
4 POSA would know as of that priority date and
5 focused in on prior art to that and began my
6 evaluation.

7 BY MS. MATTES:

8 Q. What priority date did you use?

9 A. The earliest provisional application,
10 August 21st, 2015.

11 Q. Okay. So your opinions in your
12 declaration are as of at least August 21st, 2015,
13 correct?

14 A. Yes. I was also asked to assume the
15 possibility that the priority date might be later
16 and to consider other art as of that later date.

17 Q. For purposes of ground -- if I say
18 "Ground 1," do you know what argument I'm talking
19 about?

20 A. I do.

21 Q. Okay. So for purposes of your opinions
22 with respect to Ground 1, you're using the
23 August 21 -- I'm sorry, the August 5th, 2015, date,
24 correct?

25 Oh, I'm going to say that one more time.



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1 I used the wrong date.

2 So for purposes of your opinions for --
3 with respect to Ground 1, you're using the
4 August 21st, 2015, date, correct?

5 A. I believe that's the exact date that I
6 used. I'm looking for the -- I probably stated that
7 somewhere in my report. I just want to make sure.
8 I know it's 2015 August, I just want to make sure --

9 Q. I did -- apologies. I did not mean to
10 interrupt you.

11 I did not see it in the paragraphs
12 contained in your Ground 1 explanation. However, if
13 you go to Paragraph 32 of your report, you do
14 state --

15 A. Yes.

16 Q. -- in that paragraph, "In this
17 declaration, my opinions are premised on the
18 perspective of a POSA at the time of the earliest
19 claim priority date for the '552 patents, which I
20 have been informed for this proceeding is
21 August 21st, 2015."

22 Do you see that?

23 A. I do. And the only --

24 Q. Does that help?

25 A. Yes, it was only Ground 3 that I was asked



1 to assume that the patent owner was not entitled to
2 that August 21st, 2015, priority date. And so
3 that's the basis of Ground 3.

4 Q. Okay, good. I just want to make sure
5 we're all on the same page.

6 So for Grounds 1 and Grounds 2, you're
7 opining from the perspective of a POSA as of
8 August 21st, 2015, correct?

9 A. Yes.

10 Q. And for Ground 3, you're opining from the
11 perspective of a POSA as of the later filing date,
12 which is in November 2017, correct?

13 A. That's correct.

14 Q. All right. And so before I asked how did
15 you begin your obviousness analysis, and you stated
16 that you looked at the priority date. And then you
17 thought about what prior art was in existence at
18 that time, and you began there.

19 Is that right?

20 A. Yes.

21 MR. SUH: Objection to form.

22 BY MS. MATTES:

23 Q. And what process did you -- when you say
24 "prior art," what kinds of prior art were you
25 looking at?

1 A. Well, I generally begin and use
2 Google Scholar for my searches, and so I would have
3 put in various search terms into Google Scholar.

4 I would have constrained on the year. It
5 doesn't allow you to constrain on an exact month and
6 day, so I don't know whether I would have had prior
7 to 2015 or including 2015.

8 I would generally start with prior to 2015
9 since, therefore, anything that's there I know is
10 prior art. And then I would generally also look at
11 2015 documents but making sure that they were
12 publicly available on or before August 21st.

13 I would also do a search in Google Patents
14 and, again, using a similar process.

15 And then I would also look at the file
16 history to see what the examiner considered.

17 Q. In doing your Google Scholar search, you
18 referenced that you used search terms.

19 Do you recall what search terms you used?

20 A. Well, I'm familiar with the FOLFIRINOX
21 regimen, so I certainly would have used that as a
22 search term because --

23 Q. Why?

24 A. -- because that is -- you know, that is
25 still the standard treatment for metastatic

1 pancreatic cancer, and I couldn't recall exactly
2 when that was first disclosed, so I was able to
3 figure that out in Google Scholar.

4 Google Scholar will pull up abstracts as
5 well as full publications. That's why I like it.

6 Q. And why did you start with FOLFIRINOX?

7 A. Because, in reading the claims, I said
8 this is FOLFIRINOX but with the substitution of
9 liposomal irinotecan.

10 Q. Okay. So you chose to start with
11 FOLFIRINOX because of its similarity to the claims
12 in the '552 patent, correct?

13 A. That's right.

14 Q. Besides FOLFIRINOX -- sorry. One second.

15 So in running your search in
16 Google Scholar, you had started with the claims of
17 the '552 patent to help you generate search terms,
18 correct?

19 A. Well, I needed to understand what the
20 patent was about. It was about treatment, you know,
21 of pancreatic cancer. So I needed -- you know, I
22 needed to see what was being claimed.

23 And it's like, okay, now I understand
24 what's being claimed. I didn't deal with the exact
25 dosages in my search. I just wanted to understand

1 the substance of the patent. And knowing that was a
2 Merrimack patent, and I'm familiar with Merrimack,
3 and I knew I was being retained in this matter, and
4 I knew that Ipsen owned the patent, it wasn't hard
5 for me to figure out this was a liposomal irinotecan
6 patent.

7 I'm obviously very familiar with
8 irinotecan. And I needed to know exactly what the
9 status of irinotecan development was for pancreatic
10 cancer as of the priority date, and FOLFIRINOX is
11 what comes to mind.

12 Q. And FOLFIRINOX came to mind because I
13 believe you said it was the standard treatment for
14 metastatic pancreatic cancer as of the filing
15 date -- sorry, as of the priority date for the '552
16 patent?

17 A. No, it came to mind because it's the
18 standard treatment today, and I needed to know when
19 it was first disclosed.

20 Q. Okay. So FOLFIRINOX is still the standard
21 treatment today for metastatic pancreatic cancer,
22 correct?

23 A. For the most part, yes. I mean, some
24 people will prefer to use other regimens, of course,
25 including the claimed regimen. But it's generally

1 still the preferred regimen, not necessarily at the
2 original FOLFIRINOX doses. They've been modified
3 over time.

4 Q. Do you know whether it was the standard --
5 whether FOLFIRINOX was the standard as of 2015?

6 A. I didn't actually look to see -- you know,
7 at treatment guidelines exactly at that time. I
8 actually don't know how to, you know, reliably
9 obtain old treatment guidelines such as the NCCN
10 guidelines.

11 So I can't tell you that it was the
12 standard. It was a standard.

13 Q. Right. And so then at the time, for
14 purposes of your declaration, you were not able or
15 you did not consider the NC -- the 2015 NCCN
16 guidelines for metastatic pancreatic cancer?

17 A. I don't believe I reviewed that. I, you
18 know, may be wrong. Maybe I -- you know, unless
19 it's in the list of materials I considered, I didn't
20 consider it for the purposes of my declaration.

21 Q. Okay. And if those guidelines listed
22 FOLFIRINOX as a preferred treatment, what would that
23 tell you as a POSA as of 2015?

24 A. It would tell me that it had already been
25 adopted as the preferred treatment in 2015.

1 Q. Okay. Besides FOLFIRINOX, what other
2 search terms, to the extent you recall, did you use
3 in your Google Scholar searches?

4 A. Well, I looked at reviews on the treatment
5 of metastatic pancreatic cancer from that time
6 period to see what people were writing about. And
7 generally, they were writing about FOLFIRINOX and,
8 you know, the benefits and challenges of using
9 FOLFIRINOX.

10 I looked at other regimens that were
11 similar to FOLFIRINOX, and I looked at other
12 regimens that were being used in other
13 gastrointestinal malignancies. I looked at what was
14 known about liposomal irinotecan at the time.

15 And so I did a fairly comprehensive
16 evaluation.

17 Q. And were your searches in Google Patent
18 similar in scope to the searches you ran in
19 Google Scholar?

20 A. Yes. I also had the benefit that I've
21 also been retained in a related district court case
22 on the -- on a different patent. And so I had
23 already done some searches, albeit for a different
24 patent and a different priority date.

25 Q. And what district court case is that? You



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1 said it's a related district court case.

2 Without disclosing anything confidential,
3 can you just let me know what case that is?

4 A. It's the case that's Ipsen against
5 Conjupro. I don't know what the case number is.
6 And I testified in a claim construction
7 proceeding -- not in the proceeding, but I gave a
8 deposition in, you know, in the context of the claim
9 construction for that matter.

10 Q. And when you say it's a related
11 proceeding, how was it related?

12 A. I'm sorry?

13 Q. You had mentioned that it was a related
14 case.

15 And so I guess my question is, what makes
16 it related to this IPR proceeding?

17 A. It's the same parties and the same drug.

18 Q. It's just a different patent?

19 A. Yes, and it's in district court in
20 New Jersey.

21 Q. Okay. Thank you.

22 And so after performing your searches, how
23 did you come to select the specific references
24 you're relying on for your opinions?

25 A. Well, my conclusion was that the

1 FOLFIRINOX regimen was well-established as a
2 regimen, and, therefore, it was an obvious starting
3 point for a POSA, you know, to consider.

4 And liposomal irinotecan was well-known as
5 a drug in development, and it was obvious to
6 substitute liposomal irinotecan for irinotecan. I
7 mean, that did not require, you know, much cognitive
8 input to get to that point. It was just a pretty
9 simple thing to, you know, to conclude.

10 Q. In Paragraph 26, you specifically state
11 that the challenged claims would be obvious over
12 certain references.

13 So let me know when you're at that -- at
14 that paragraph because I have a few questions.

15 A. It's Paragraph 26?

16 Q. Correct.

17 A. Yes, I'm there.

18 Q. So in Paragraph 26, you list that the
19 challenged claims would have been obvious over
20 Conroy, correct?

21 A. Yes.

22 Q. And what is Conroy?

23 A. Conroy is a "New England Journal of
24 Medicine" paper that ascribes the results of an
25 investigator-initiated Phase 3 trial of FOLFIRINOX



1 compared to gemcitabine.

2 Q. Is Conroy considered to be one of the
3 preeminent, I guess, studies that made FOLFIRINOX a
4 drug that practitioners wanted to give to patients
5 with metastatic pancreatic cancer?

6 Is this kind of -- is the Conroy
7 publication the seminal publication for FOLFIRINOX?

8 MR. SUH: Objection to form.

9 You may answer.

10 THE WITNESS: Well, I don't know what you
11 mean by "the seminal publication," you know.

12 There are many seminal publications that
13 led up to the development of the FOLFIRINOX
14 regimen. So it's a regimen. And the regimen
15 was taken forward, you know, and developed and
16 basically was the FOLFIRI regimen with
17 oxaliplatin added to it.

18 And oxaliplatin was a known active agent
19 in colorectal cancer, and FOLFIRI was the
20 standard regimen for colorectal cancer, and the
21 FOLFOX regimen was a standard regimen for
22 colorectal cancer.

23 So it's like FOLFOX and FOLFIRI got
24 together and gave birth to FOLFOX --
25 FOLFIRINOX. It also gave birth to its sibling,

1 FOLFOXIRI. And then this regimen was pushed
2 forward into pancreatic cancer as -- given the
3 dearth of effective treatments for pancreatic
4 cancer.

5 BY MS. MATTES:

6 Q. And then in this paragraph you also list
7 Mahaseth, correct?

8 A. Yes.

9 Q. Why did you select the Mahaseth
10 publication?

11 A. Mahaseth is a publication that explicitly
12 teaches dropping the 5-fluorouracil bolus, which is
13 really the way FOLFIRINOX is given today, well,
14 modified FOLFIRINOX, and that's really the standard.

15 But it was that paper that was the first
16 paper to explicitly teach that.

17 Q. (Audio distortion.)

18 (Stenographer clarification.)

19 BY MS. MATTES:

20 Q. Dr. Ratain, you're able to hear me?

21 A. I can now.

22 Q. Okay. Please let me know if there's any
23 hiccups. I appreciate it.

24 A. I didn't catch that, though.

25 Q. Please let me know if there's any

1 interruptions or disruptions, and I will try my best
2 to figure out what's going on.

3 A. Seems to be your head position.

4 Q. Okay. If we go -- (audio distortion).

5 (Stenographer clarification.)

6 MS. MATTES: Let's go off the record for a
7 second.

8 (Whereupon, a recess was taken
9 from 9:39 a.m. to 9:44 a.m.)

10 MS. MATTES: We can go back on the record.

11 BY MS. MATTES:

12 Q. Before we took our break, Dr. Ratain, I
13 asked, "Why did you select the Mahaseth
14 publication?"

15 Do you recall that?

16 A. I do.

17 Q. And you stated, "Because it was a
18 publication that explicitly taught dropping the
19 5-fluorouracil bolus."

20 Do you remember that?

21 A. Yes.

22 Q. Why were you looking at a publication that
23 was specifically teaching dropping the
24 5-fluorouracil bolus?

25 A. Because, one, when I read the

1 specification, they made a point of that, the
2 patentees.

3 And, two, because I was aware that it's --
4 it's been dropped from the FOLFIRINOX regimen by the
5 vast majority of clinicians.

6 Q. Okay. So the reasons why you were looking
7 for references that taught dropping the
8 5-fluorouracil bolus was because the '552 patent
9 specification made a point of that -- of that
10 modification, as well as you had read about that
11 5-fluorouracil bolus having been dropped from the
12 FOLFIRINOX regimen as well, correct?

13 MR. SUH: Objection to form -- I'm sorry.
14 Objection to form.

15 THE WITNESS: I need to understand the
16 evolution of the modern FOLFIRINOX regimen, the
17 other work that had been done suggesting
18 modifications to the regimen since it was first
19 developed.

20 So I had to sort of develop all of that
21 history, so to speak. There's not a paper out
22 there that describes the history of the
23 FOLFIRINOX regimen. So I basically had to
24 construct that up until the priority date and
25 understand the history there.

1 Some of that was described in the
2 specification itself as background. Some of it
3 was described in the examples, for example,
4 as -- you know, even though it was history.

5 So I needed to understand what was known
6 and what was done by the alleged inventors.

7 BY MS. MATTES:

8 Q. Okay. So I think I understand what your
9 thought process was then.

10 So then one of the reasons you were
11 looking for that specific modification was because
12 the '552 patent specification had discussed the
13 background of FOLFIRINOX and other kinds of
14 modifications of FOLFIRINOX.

15 And one of those modifications was the
16 removal of the 5-FU, or fluorouracil bolus dose,
17 correct?

18 MR. SUH: Objection to form.

19 THE WITNESS: And I do note, as I'm taking
20 another look at the background, that the
21 background states that FOLFIRINOX was a
22 preferred option, but it doesn't say "the
23 preferred," "a preferred" option since 2011.

24 And the background also notes that in
25 Column 2, Lines 3 to 6, that modified

1 FOLFIRINOX regimens are often used, including
2 elimination of the 5-FU bolus.

3 So that was listed there, and, you know,
4 unfortunately, I couldn't rely on the list of
5 publications in the patent itself because it
6 was -- it would be like finding a needle in a
7 haystack.

8 BY MS. MATTES:

9 Q. Understood. Okay. Going back to
10 Paragraph 26 of your expert declaration, you can
11 imagine I have similar questions for the other
12 references cited here.

13 So you also list Bayever as a publication
14 you're relying on in support of your opinions,
15 correct?

16 A. Yes.

17 Q. And why did you select Bayever?

18 A. Because Bayever taught the use of
19 liposomal irinotecan in combination with 5-FU and
20 leucovorin, so taking the FOLFIRI regimen and
21 substituting in irinotecan -- substituting liposomal
22 irinotecan for irinotecan.

23 Q. Okay. And then you have here the Saif
24 publication.

25 Why did you select the Saif publication?



1 A. It was -- when I was searching for
2 publications that discussed liposomal irinotecan, it
3 was one of the publications that came up, so I read
4 every paper that discussed liposomal irinotecan.

5 Q. And of all those papers, you chose Bayever
6 and Saif, correct?

7 A. And Ko.

8 Q. And Ko, excuse me, you're right.

9 So out of the references that you reviewed
10 that discussed liposomal irinotecan, you chose to
11 rely on Saif, Bayever, and Ko, correct?

12 A. Yes. I don't think I missed any prior art
13 that were relevant, but I'd be happy to be
14 corrected.

15 There was a lot of prior art.

16 Q. I'm not -- I'm not --

17 A. There was a lot of prior art --

18 Q. I'm not suggesting --

19 A. -- in my opinions. It was challenging to
20 narrow it down.

21 Q. I'm not suggesting you missed anything.
22 I'm just trying to make sure that I'm understanding
23 what your opinions are.

24 And then for Cantore, why did you select
25 Cantore?

1 A. I have to refresh my memory on Cantore. I
2 believe that was one of the ones that was after the
3 2015 priority date.

4 It would be helpful if I could look at
5 that document, Counsel.

6 (Exhibit 1009 was marked for
7 identification.)

8 BY MS. MATTES:

9 Q. Sure. You can definitely do that. In
10 case it's helpful to you, you have a Table of
11 Contents for your expert report -- oh, I see what
12 you're saying, yes.

13 But it is Exhibit 1009, and it should be
14 in your box, if it's helpful.

15 A. Thank you.

16 So this regimen, Cantore, it discloses
17 just the use of two of the drugs, irinotecan and
18 oxaliplatin, but it's a much older reference. So
19 it's part of the ancestry, so to speak, of
20 FOLFIRINOX, and that's why I looked at it.

21 It also -- counsel asked me are there any
22 references to specifically disclose an oxaliplatin
23 dose of 60 milligrams per meter squared, and so I
24 found this regimen.

25 And so it's part of the history here, and



1 it also has that specific dose.

2 Q. And you were looking for the specific dose
3 of 60 milligrams per meter squared of oxaliplatin,
4 because that's the dose -- the dose recited in
5 claim 1 of the '552 patent, correct?

6 A. Counsel asked me if there was -- were any
7 publications that disclosed it. I didn't feel it
8 was necessary because I knew that dose had been
9 used; for example, you know, the dose reduction in
10 Conroy.

11 But counsel asked me if there were any
12 publications along those lines. I don't -- wouldn't
13 have needed this reference. It's not critical to my
14 opinions. If this reference had never been
15 published, it wouldn't change my opinions in any
16 way, shape, or form.

17 Q. What do you mean when you reference -- or
18 what are you referring to when you reference the
19 "dose reduction in Conroy"?

20 A. I'm referencing the dose reduction that's
21 described in the protocol as a "dose reduction" and
22 explicitly taught in the protocol itself as well as
23 in the appendix.

24 And so the protocol is, you know, critical
25 to understanding any Phase 3 or, for that matter,

1 any study. It's critical to review the protocol,
2 which is why most top journals require that the
3 protocol be submitted at the time of initial
4 submission, and it's always published alongside any
5 major paper. For most journals, not all.
6 Certainly, New England Journal of Medicine does
7 that.

8 We're adjusting the temperature in here,
9 in case you're wondering what else is going on in
10 this room. I'm a little cold.

11 Q. And the Conroy protocol has a dose
12 adjustment to 60 milligrams per meter squared, is
13 what you're -- sorry. Strike that.

14 From what dose -- in the Conroy protocol,
15 from what dose is the dose adjusted to 60 milligrams
16 per meter squared of oxaliplatin?

17 MR. SUH: Objection to form.

18 THE WITNESS: Are you asking what's the
19 starting dose?

20 BY MS. MATTES:

21 Q. Correct.

22 A. The starting dose was 85, and
23 oxaliplatin --

24 Q. And --

25 A. I'm sorry.



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1 Q. No, continue. I did not mean to cut you
2 off. Sometimes, Zoom, it's hard. You can't talk
3 over each other, so --

4 A. Yes, it's common to reduce doses of
5 oxaliplatin, and it's notorious for causing
6 neurotoxicity. And so it's -- again, many
7 practitioners just choose to reduce it at the start
8 rather than waiting until the patient has trouble
9 walking. They prefer to prevent that problem by
10 using lower doses in the first place.

11 Q. The Conroy protocol has the 85 milligrams
12 per meter squared oxaliplatin as the starting dose,
13 correct?

14 A. Yes.

15 Q. And then it instructs practitioners or
16 doctors to reduce that dose to 60 milligrams per
17 meter squared, depending on certain -- I guess
18 certain toxicities that may occur in a patient,
19 correct?

20 A. Right. It increases both the toxicity,
21 the myelosuppression, particularly the irinotecan,
22 as well as it's a -- you know, can cause severe,
23 disabling neurotoxicity.

24 Q. Okay. Understood. You had stated earlier
25 that in addition -- let me start over.

1 You had stated earlier that you had also
2 reviewed the file history of the '552 patent to see
3 what references the examiner had relied on as well.

4 Did I -- did I get that correctly?

5 A. Yes. As part of a comprehensive search, I
6 wanted to make sure I wasn't missing anything. If
7 the examiner had relied on something that I was
8 missing, hadn't considered yet, I wanted to make
9 sure I looked at that as well.

10 And I needed to understand how this
11 patent -- which I viewed as very obvious at this
12 point, you know, before I looked at the file
13 history -- how it had even been allowed.

14 Q. Okay. And did you take into consideration
15 whether any of the references you relied on were
16 already considered by the examiner during
17 prosecution?

18 MR. SUH: Objection to form.

19 THE WITNESS: I was pleased to see that
20 the examiner's thinking was very similar to my
21 own, up until they got to the question of
22 unexpected results, where things fell apart,
23 from my perspective, in the patent office.

24 BY MS. MATTES:

25 Q. Okay. Let's go to Paragraph 229 of your



1 expert report. This is where you -- it's under the
2 section of your report called "Unpatentability of
3 the '552 Patent."

4 Let me know when you're there.

5 A. I'm there.

6 Q. Okay. And so here is where you set forth
7 your opinions with respect to Ground 1, correct?

8 A. Yes.

9 Q. Okay. And your opinions with respect to
10 Ground 1 seem to span from Paragraph 229 through --
11 I'm making sure we're on the same page -- through
12 Paragraph 307, correct, which takes you through
13 Page 120 of your declaration?

14 A. Counsel, it seems to go through -- claim 1
15 goes through -- my discussion goes through
16 Paragraph 264 on Page 108 on claim 1.

17 Or you mean the whole -- and then I go
18 into other -- the other claims as well, yes. You're
19 correct.

20 Q. Yeah, I was being -- I was being
21 comprehensive of all the challenged claims.

22 But you are right. For purposes of
23 claim 1, your opinion goes through Paragraph 264.

24 A. Right.

25 Q. I think we're on the same page.



1 A. Yes, we are.

2 Q. Okay. Good. So these are long reports,
3 so I kind of like to set the boundaries of what
4 we're talking about.

5 A. There was a lot of prior art.

6 Q. Yes. Okay. So if we go back to -- since
7 we covered a lot of pages, if we go back to this
8 Page 95 of your report, here is where you say
9 claim 1 would have been obvious over Conroy, the
10 Conroy protocol, and Mahaseth, in combination with
11 the knowledge and skill of the POSA, including
12 Bayever, Saif, Ko, and Cantore.

13 Do you see that? I'm just reading the
14 heading of -- the heading of A on that page.

15 A. Yes.

16 Q. Okay. And --

17 MR. SUH: Objection to form. Sorry.

18 BY MS. MATTES:

19 Q. So Conroy -- that's okay.

20 Conroy, Conroy protocol, Mahaseth,
21 Bayever, Saif, Ko, and Cantore, are these the main
22 references you're relying on for your obviousness
23 opinion?

24 A. Well, I mean, quite frankly, I really only
25 need Conroy, but these others are -- you know, make



1 it very, very clear.

2 Conroy protocol is very helpful if one
3 needs to get to very specific doses, but it's very
4 obvious. A POSA is well aware of how to reduce
5 doses for toxicity, including all the modifications
6 that were made, the obvious modifications by
7 Mahaseth, and, you know, the teachings of these
8 other references.

9 And then the liposomal irinotecan
10 references, at least one of those is important
11 because the POSA needs to be aware of liposomal
12 irinotecan and something about its properties, which
13 are very similar, you know, to lipo- -- to
14 irinotecan when given by a prolonged infusion.

15 Q. Okay. Let's go to Paragraph 232 of your
16 report.

17 Here you state that the claimed
18 invention -- excuse me. Here you state that
19 "Claim 1 would have been obvious over the prior art
20 at least because the claimed method of treatment
21 involved administering an antineoplastic therapy
22 consisting of liposomal irinotecan, oxaliplatin, and
23 5-fluorouracil, the same four-drug combination as in
24 the established gold standard FOLFIRINOX regimen for
25 first-line treatment of metastatic pancreatic



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1 cancer."

2 Do you see that?

3 A. I do.

4 Q. Okay. So is it your opinion that one of
5 the reasons why the claimed invention is obvious is
6 because the FOLFIRINOX regimen has the same four
7 drugs as what's claimed in the '552 patent?

8 A. Well, if you consider liposomal irinotecan
9 and irinotecan to be the same drug with the liposome
10 just representing a different way of administering
11 irinotecan, yes.

12 Q. I see. Well, I'm just using your words.
13 You wrote "the same four-drug combination."

14 So is it your opinion that those two drugs
15 are the same drugs?

16 A. Well, they're the same drugs, so to speak.
17 They're the same active therapy.

18 In other words, the liposome represents a
19 different way of administering irinotecan. If the
20 irinotecan had been administered as a 96-hour
21 infusion, for example, I would also say it's the
22 same four-drug regimen, even though it's a different
23 way of administering irinotecan.

24 So I'm using "drug" in a broad sense as
25 opposed to a pharmaceutical product.

1 Q. Okay. So you're using "drug" as referring
2 to the active ingredient as opposed to what is
3 sometimes referred to as a "drug product"?

4 A. Right. I'm not referring to the drug
5 product. I'm referring to the active pharmaceutical
6 ingredient here.

7 Q. Right. And liposomal irinotecan has its
8 own distinct FDA labeling, correct?

9 A. Yes, and it's a distinct product, and it
10 has similar but different properties from free
11 irinotecan. But they're certainly siblings or
12 father-child relationship.

13 Q. What are the different properties between
14 liposomal irinotecan?

15 And if I say "free" -- should I say
16 "irinotecan"? Or I don't want to confuse us on the
17 record.

18 So do you prefer "free irinotecan" or just
19 saying "irinotecan"?

20 A. Well, I have an idea. Why don't we
21 call -- to simplify things, why don't we refer to
22 irinotecan as "irinotecan," and either for
23 liposomal, either say "liposomal irinotecan" or
24 "Onivyde."

25 And I'm comfortable with that. That way,

1 we won't get confused.

2 Q. Sure.

3 A. And so Onivyde is -- you know, has
4 different pharmacokinetics, and it results in
5 basically a sustained release of irinotecan. And
6 that changes the schedule of irinotecan in a way
7 that basically means that the potency per milligram
8 of irinotecan is greater in the Onivyde product
9 because the effects of irinotecan are highly
10 dependent on schedule.

11 But if you give a small amount over a
12 period of time, that has a greater effect than
13 giving that same total dose all at once. And so
14 that's the different properties.

15 And this is something I've written about
16 extensively in the past. I wrote many -- the first
17 clinical trial I ever did was continuous infusion
18 chemotherapy of an anticancer drug, and I wrote many
19 book chapters on that topic well before irinotecan
20 was discovered.

21 So the notion of giving drugs by slow
22 infusion has been well-understood for decades.

23 Q. When you say "highly dependent on
24 schedule," what does that mean?

25 A. In other words, there have been studies in

1 the past of giving irinotecan by prolonged infusion,
2 and you can only -- if you give a very small amount
3 every day, it's toxic, just because you've got the
4 drug around continuously, and, therefore, it has a
5 greater effect.

6 So liposomal irinotecan has properties
7 similar to prolonged infusion of irinotecan. And
8 what's unclear is whether liposomal irinotecan can
9 increase the efficacy of irinotecan. It's just not
10 entirely clear.

11 There's some preclinical studies that
12 certainly suggest that. There was certainly
13 enthusiasm for that possibility, just like there was
14 enthusiasm for encapsulating paclitaxel, and that
15 led to the development of ABRAXANE.

16 But, you know, it's not yet been proven
17 that this formulation or this schedule of giving
18 irinotecan, so to speak, is superior than the more
19 conventional, historical approach.

20 Q. Is that true as of today?

21 A. Yes.

22 Q. Okay. And so that would have been true as
23 of August 21st, 2015, as well?

24 A. Yes.

25 Q. Okay. So let's keep going through your

1 expert declaration.

2 And so in Paragraph 233, here, you list
3 out the FOLFIRINOX regimen as taught by Conroy,
4 correct?

5 A. Yes.

6 Q. And then you go on to explain why a POSA
7 would have been modified -- excuse me, why a POSA
8 would have been motivated to modify the FOLFIRINOX
9 regimen; is that right?

10 MR. SUH: Objection to form.

11 THE WITNESS: Well, that's what a --
12 that's what I discuss further, and there were
13 motivations to modifying, including dosage
14 reductions.

15 That's also described in one of the
16 references that I didn't cite but you kindly
17 provided in response in one of your briefs, the
18 Marsh reference. It also discusses all of the
19 modifications to FOLFIRINOX. And I appreciated
20 you providing that because it's a very nice
21 summary.

22 BY MS. MATTES:

23 Q. Okay. And so, in your opinion, what
24 were -- what was the main -- or what were the
25 motivations that you're relying on -- actually,

1 strike that. I want to start with the modification.

2 What are the proposed modifications to the
3 FOLFIRINOX regimen that you believe were obvious to
4 do?

5 A. Well, the two modifications are to make it
6 work better and to make it less toxic. Those were
7 the -- the two goals of anybody modifying a regimen.

8 Q. So maybe I think I confused you because I
9 switched the use of my words.

10 So what you're responding to is what were
11 a POSA's motivation to modify the FOLFIRINOX
12 regimen; is that correct?

13 A. I thought that was what you asked me.

14 Q. I'd asked what were the modifications, but
15 that's -- it's okay. We can start with motivation.

16 So in your opinion, there were two
17 motivations to modify the FOLFIRINOX regimen.

18 One was to reduce toxicity, correct?

19 A. Yes.

20 Q. Okay. And the second was to make a -- I
21 think you used the words "make a better product"; is
22 that right?

23 A. Well, nobody is getting cured with
24 FOLFIRINOX. So patients are all dying of metastatic
25 pancreatic cancer, and they're often -- sometimes

1 they're dying of side effects of treatment. And --
2 but it was better than what we had before. We had
3 only gemcitabine really. Erlotinib was approved for
4 pancreatic cancer, but nobody prescribed that.

5 And irinotecan was known to be an active
6 drug. Of course, 5-FU and leucovorin had some
7 activity. But there was really not much you could
8 do with these patients other than generally enroll
9 them in a clinical trial.

10 So FOLFIRINOX came along, and it was
11 great, you know. The regimen was effective if it
12 didn't kill you.

13 So -- but the challenge was reducing the
14 morbidity and mortality of FOLFIRINOX. And at the
15 same time, it was good, but it wasn't great. You
16 still were going to die of your pancreatic cancer.

17 So that was really what -- the way a POSA
18 would look at that regimen and the state-of-the-art
19 of pancreatic cancer at the August 2015 priority
20 date.

21 Q. So, in your opinion, they would be looking
22 to -- excuse me.

23 They would be looking to reduce toxicity
24 of the FOLFIRINOX regimen, and then what would -- I
25 understand that they would be motivated to make

1 something better.

2 But what exactly -- I guess, what are the
3 criteria that a POSA would be looking at for that
4 second motivation?

5 MR. SUH: Objection to form.

6 THE WITNESS: Well, there would be a
7 couple of approaches.

8 So, one, if you could add a drug that
9 didn't add to the side effects of FOLFIRINOX,
10 that would be one possibility.

11 You could give drugs such as
12 colony-stimulating factors to reduce the side
13 effects of FOLFIRINOX. That was widely used
14 anyway.

15 And then liposomal irinotecan was another
16 attractive consideration because of the
17 suggestion in the preclinical studies, the
18 Bayever patent, that it was better than
19 irinotecan.

20 And so the hypothesis that Onivyde -- or
21 it wasn't known as Onivyde then, but the
22 liposomal irinotecan was better than irinotecan
23 was worth testing.

24 And, unfortunately, it's not been
25 rigorously tested. It's never been rigorously



1 tested in any clinical trial to get the answer
2 to that question.

3 BY MS. MATTES:

4 Q. What hasn't been vigorously -- rigorously
5 tested exactly?

6 A. Well, for example, you know, the -- you
7 know, one could compare in second-line therapy the
8 use of the approved liposomal
9 irinotecan/5-FU/leucovorin regimen to the FOLFIRI
10 regimen in a randomized trial. That's never been
11 done. The randomized trial only used FU/leucovorin
12 as the control arm.

13 One could compare the NALIRIFOX regimen
14 that's the subject of the claims here in a
15 prospective randomized trial to the FOLFIRINOX
16 regimen. That's not been done.

17 One could compare a liposomal
18 irinotecan-containing regimen to a
19 irinotecan-containing regimen in a different
20 disease, such as colorectal cancer or gastric
21 cancer. That's never been done.

22 So there has been no rigorous testing of
23 the hypothesis. And such studies are generally done
24 by pharmaceutical companies after they get their
25 drug approved to promote the use of their product

1 because many -- you know, to address concerns that
2 the product doesn't -- you know, isn't worth the
3 extra cost, yet that's not been done.

4 Q. I see what you're saying.

5 There hasn't been a study done that
6 directly compares liposomal irinotecan either alone
7 or in a combination regimen against irinotecan alone
8 or in a comparable combination regimen?

9 Am I understanding you correctly?

10 A. Yes. Other than one very small trial
11 early in the development that was done in gastric
12 cancer, there's really been -- that's the only trial
13 I'm aware of in which there was a randomization.
14 And that trial was too small to be definitive, and
15 it was hard to interpret the results of that study.

16 So, really, there's not the trial that
17 rigorous, rigorous oncologists are looking for to
18 sort of cut through marketing hype and everything
19 else. And, you know, you look for -- at some point,
20 you've just got to bite the bullet and do the trial,
21 and -- but there hasn't been an interest in doing
22 that, at least that I'm aware of.

23 I don't know whether the company has been
24 approached by investigators, but I certainly have
25 seen no such trial ever appear. And I even looked

1 just recently to see if possibly such a trial was in
2 development on clinicaltrials.gov, and there isn't
3 any such trial.

4 Q. You had referenced one very small trial
5 earlier.

6 Do you recall if that trial is the Roy
7 publication that you had included as part of your
8 expert declaration?

9 It is -- I will tell you in a second. I
10 believe it is Exhibit 1055, so that should be in
11 your box.

12 (Exhibit 1055 was marked for
13 identification.)

14 MR. SUH: So objection to form.

15 THE WITNESS: We will pull that exhibit.
16 Yes, that's the study.

17 BY MS. MATTES:

18 Q. Okay. And so this is the study that you
19 stated was too small to be definitive, and it was
20 hard to interpret the results of this study,
21 correct?

22 A. That's right.

23 Q. Okay. You can put that study to the side.
24 I appreciate the explanation. This is
25 very helpful to understand all of that.

1 Is it fair to say that in your opinion, a
2 POSA, then, would be motivated by, one, reducing
3 toxicity in order to reduce side effects, and, two,
4 by the properties of liposomal irinotecan that were
5 known at the time of the priority date?

6 MR. SUH: Objection to form.

7 You may answer.

8 THE WITNESS: I'm not sure. I didn't
9 fully understand the question.

10 BY MS. MATTES:

11 Q. Sure. You provided a lot of explanation.
12 I'm trying to just kind of figure out what your two
13 motivations are for modifying the FOLFIRINOX
14 regimen.

15 So to me, it sounds like you're saying a
16 POSA would have been motivated to modify the regimen
17 based on, one, wanting to reduce toxicity in the
18 form of reducing side effects; is that right?

19 A. Yes.

20 Q. Okay. And then, two, they would have been
21 motivated based on the properties of liposomal
22 irinotecan that were known as of August 2015; is
23 that right?

24 A. Well, that's -- yes, but that's if you
25 wanted to substitute liposomal irinotecan.



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1 There were other modifications one could,
2 in theory, make. I mean, if there was some
3 promising new kinase inhibitor or monoclonal
4 antibody that, you know, wouldn't substantially
5 increase side effects, and particularly, if you
6 reduce some of the other doses, you could do that.

7 So, I mean, there were things -- I mean,
8 one of my colleagues was developing a regimen where
9 trying to add paclitaxel to the FOLFIRINOX regimen
10 for use in gastric cancer but was reducing doses of
11 the other drugs.

12 So I think there's lots of -- it's kind of
13 like cooking. And that's why these are recipes --
14 oncologists refer to them as "recipes" -- where you
15 have your ingredients in your kitchen, and you have
16 to decide, you know, what to do. And if you're --
17 if the ingredients are seasonings and you're cooking
18 a stew or soup, and you've got to taste as you go
19 along to make sure it doesn't get too salty or too
20 spicy, and you adjust it, it's the same thing with
21 these chemotherapy regimens.

22 It's just one -- you know, sometimes in
23 clinical -- routine clinical practice, oncologists
24 just make these changes on their own. And there's
25 some examples of that in the literature, even, in

1 regard to the NALIRIFOX regimen -- or the FOLFIRINOX
2 regimen, rather.

3 And then sometimes oncologists do this in
4 the context of rigorous clinical trials, and then
5 it's written down and all tested prospectively.

6 Q. I kind of like this cooking -- this
7 cooking analogy. It helps put your opinions in
8 perspective for me.

9 One of the things you mentioned is, you
10 know, as you're going through this, or as you're
11 cooking, you would taste -- you would taste along
12 the way, or you would add a spice or add a
13 seasoning, and then you would kind of taste it to
14 see how it goes.

15 I guess, in your mind, how does that apply
16 to this modification? Does that mean -- sorry, go
17 ahead.

18 MR. SUH: Objection to form.

19 THE WITNESS: Well, that's exactly what is
20 done in the Phase 1 trials that we're -- of the
21 combination. Whether you're looking at the
22 Bayever patent or you're looking at the '552
23 patent, both of them write a protocol where
24 you're tasting as you go along.

25 And you go, well, we think we can get this

1 dose in, but it might make it too toxic. Well,
2 we want to put this new pepper I bought in, but
3 it might make it too spicy.

4 So it's the same thing. It's just like
5 cooking. Can we add this? Can we add this?
6 Well, how much can we add? Do we have to cut
7 something else back if we want to add this?

8 Now, I've got this great new smoked
9 pepper, but, you know, I'm going to have to cut
10 the Thai peppers down.

11 BY MS. MATTES:

12 Q. And so when a person of skill in the art
13 makes one modification, they would then test that
14 modification to see how it -- how it works, correct,
15 before making another modification?

16 A. Well, that's generally -- that's called a
17 Phase 1 protocol. Whether your -- you know, so
18 particularly for Phase 1 combinations, if you're
19 trying to determine a maximum dose, a maximum dose
20 for any combination, there's actually an infinite
21 number of possibilities, because if you turn up one
22 drug, you can add more of a second drug or a third
23 drug.

24 So it's basically a cooking experiment as
25 opposed to an experiment where you're trying to find

1 the maximally tolerated dose of a single drug.
2 That's like a mountain-climbing expedition. Where
3 is the top of the mountain?

4 So -- but these are -- they're both,
5 they're both routine. Neither one tries to find an
6 optimal dose. These clinical trials only define --
7 try and define a maximum tolerated dose or set of
8 doses.

9 And as I said, with the combination, if
10 you want to add liposomal irinotecan to oxaliplatin
11 and 5-FU-leucovorin, and you say, well, I want the
12 dose -- the combination to be the maximum -- a
13 maximum dosage that people can tolerate but doesn't
14 kill anybody, well, there's an infinite number of
15 possibilities to do that.

16 Q. So if a person of ordinary skill in the
17 art wanted to modify the FOLFIRINOX regimen by
18 adding liposomal irinotecan -- or, excuse me,
19 replacing irinotecan with liposomal irinotecan, is
20 it your opinion, then, that there's a maximum number
21 or an infinite number of possibilities as to what
22 the dose --

23 A. Well, I'm --

24 Q. -- would be used?

25 I guess I'm not sure what --

1 MR. SUH: Objection to form.

2 But go ahead.

3 THE WITNESS: I'm talking as a
4 mathematician, not as a practical matter.

5 As a practical matter, you know, you know
6 you're going to be -- you're developing a
7 regimen for physicians that -- you know, you're
8 not going to be using doses of
9 61.7325 milligrams. So as a practical matter,
10 you're going to use round numbers, you know.

11 You're going to use a stepwise approach,
12 and because that's -- you know, if you came up
13 with some very precise, weird number, everybody
14 would say, "Why are you doing that? That just
15 is going to confuse people." I was speaking
16 mathematically.

17 BY MS. MATTES:

18 Q. Understood. So from a practical
19 perspective, if a person of skill in the art were to
20 modify the FOLFIRINOX regimen by replacing
21 irinotecan with liposomal irinotecan, what would be
22 the next step?

23 MR. SUH: Objection to form.

24 BY MS. MATTES:

25 Q. How would a --

1 A. Well, it depends what they knew. If
2 you're asking me what was known in 2015, in
3 August 2015, well, Bayever basically teaches you the
4 doses of liposomal irinotecan you can give with 5-FU
5 and leucovorin, okay.

6 And, well, you could say, all right, how
7 did we get to a regimen that includes -- and then --
8 and let's just say we're trying to modify
9 FOLFIRINOX, so you have to add your oxaliplatin to
10 that. So you would say, okay, when they created
11 FOLFIRINOX, you know, they took the FOLFIRI regimen,
12 and then they added oxaliplatin at 85 milligrams per
13 meter squared. Well, we -- let's see if we can add
14 85 milligrams per meter squared to Bayever.

15 And when they found that there was too
16 much toxicity, they said, okay, we can't do that.
17 And that -- part of that is also because, you know,
18 the dose of irinotecan is going to be variable, too.

19 So you have to -- if you're -- you're
20 changing your doses of liposomal irinotecan, you're
21 changing your doses of oxaliplatin. And so you
22 write a protocol where you start conservatively, and
23 you figure out, okay, where do we want to get to
24 with the irinotecan, and how much oxaliplatin can we
25 get in?



1 Q. I may have missed -- I just want to make
2 sure I understood something that you just said.

3 You had said that when they -- when they
4 created FOLFIRINOX, they took -- I'm sorry.

5 When they created FOLFIRINOX, they started
6 with, I guess, the FOLFIRI regimen, and they added
7 oxaliplatin at 85 milligrams per meter squared,
8 correct --

9 A. Yes. That is -- that it is --

10 Q. -- for that regimen? Okay.

11 A. That is FOLFIRINOX. It's FOLFIRI --

12 Q. Okay.

13 A. -- plus 85 per meter squared of
14 oxaliplatin.

15 Q. I see. And then you said, well, then
16 let's see if we can add 85 millimeters [sic] per
17 meter squared to Bayever, and then they found that
18 there was too much -- too much toxicity.

19 Do you recall saying that just now?

20 A. Yes.

21 Q. Okay. I guess what -- where in the prior
22 art had someone added 85 milligrams per meter
23 squared of oxaliplatin to Bayever --

24 A. Well, that was --

25 Q. -- and found that there was too much --

1 A. That was --

2 Q. -- and found that there was too much
3 toxicity?

4 MR. SUH: Objection to form.

5 THE WITNESS: I'm reading from Example 3
6 in the patent. Okay. It talks about the
7 target dose of oxaliplatin, 60 to 85 milligrams
8 per meter squared.

9 BY MS. MATTES:

10 Q. Right. But that's our '552 patent,
11 correct?

12 A. Yes. No, I didn't say in the prior art.

13 Q. So as of --

14 A. I wasn't referring to prior art. You
15 asked me -- you asked me how -- how one would do
16 that.

17 Q. Right. I see the confusion. Apologies.
18 I should have been more clear.

19 I guess my question was in the context of
20 as of August 2015, right, without knowledge of our
21 claimed invention, right, so as of August 2015 --
22 let me just go back to what my original question was
23 so we can start over again.

24 So I'll re-ask my question with that point
25 of clarity.



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1 So as of August 21st, 2015, from a
2 practical perspective, if a POSA were to modify the
3 FOLFIRINOX regimen by replacing irinotecan with
4 liposomal irinotecan, what would be the next step
5 that a POSA would take?

6 MR. SUH: Objection to form.

7 THE WITNESS: As I said, they could start
8 with Bayever and then add oxaliplatin to it,
9 hoping that they could get an 85 milligrams per
10 meter squared, exactly what was done here in
11 the -- in Example 3.

12 BY MS. MATTES:

13 Q. And so if the results -- so when a POSA
14 makes that modification, adds oxaliplatin to
15 Bayever, they would have to test that combination in
16 order to determine whether -- whether there were any
17 toxicity issues, correct?

18 MR. SUH: Objection to form.

19 THE WITNESS: Sure. That's the routine
20 experimentation of any Phase 1 trial, and you
21 decide what doses you want to start with, you
22 know, and you know you could be more precise as
23 far as how you do your irinotecan dosing.

24 It's well-known that the toxicity of
25 irinotecan is highly dependent on UGT1A1

1 genotype --

2 BY MS. MATTES:

3 Q. Right.

4 A. -- so you might do your genotyping before
5 you dose so you get, you know -- and so there's lots
6 of ways you can do it exactly, but the general
7 concept would be to take Bayever and hope you can
8 add in 85 per meter squared of oxaliplatin. And if
9 you can't, you can't. But, you know, you know that
10 60 milligrams per meter squared is a commonly used
11 dose, and that's fine, too.

12 MR. SUH: Excuse me, Counsel. I'm sorry,
13 Counsel. We've been going for more than an
14 hour since the last break.

15 Is this a good time for a break? Do you
16 want to ask --

17 MS. MATTES: I would like to just maybe
18 wrap up this line, maybe a couple more minutes.
19 Is that okay with you?

20 MR. SUH: Sure.

21 MS. MATTES: Okay, great.

22 BY MS. MATTES:

23 Q. Let me just go back to my question before
24 so I can get back on track.

25 And, Dr. Ratain, Bayever doesn't discuss

1 oxaliplatin, correct?

2 A. It's not claimed. I can't remember
3 whether it discusses it. I'd have to look at the
4 document to tell you whether it discussed.

5 Q. Okay. Do you recall whether Bayever
6 teaches a person of skill in the art to use
7 liposomal irinotecan with oxaliplatin?

8 A. I'd be happy to look at that document and
9 give you an answer to that question.

10 (Exhibit 1006 was marked for
11 identification.)

12 BY MS. MATTES:

13 Q. Sure. If you pull out Exhibit 1006.

14 A. Well, the simple -- using the broadest
15 definition of "teach," the answer is yes.

16 Q. What do you mean, "using the broadest
17 definition of 'teach'?"

18 A. If you look in the background, the third
19 paragraph, it describes FOLFOX. It describes
20 FOLFIRINOX.

21 Q. Okay.

22 A. So it teaches a POSA about the use of
23 oxaliplatin in the treatment of pancreatic cancer.
24 It treats -- it teaches a POSA about the use of
25 oxaliplatin in combination with irinotecan, and not

1 that a POSA needed this teaching because Conroy was
2 published in 2011.

3 So it's all in there, and, you know, so it
4 teaches that.

5 Q. Bayever does not expressly recite the use
6 of a combination therapy using liposomal irinotecan
7 with oxaliplatin, correct?

8 MR. SUH: Objection to form.

9 THE WITNESS: No, but it would -- it's
10 obvious to do that if a POSA is aware of
11 liposomal irinotecan.

12 BY MS. MATTES:

13 Q. But Bayever expressly doesn't disclose
14 that, correct?

15 A. Correct.

16 MS. MATTES: Okay. I think we can take a
17 break. Thank you.

18 THE WITNESS: Thank you.

19 (Whereupon, a recess was taken
20 from 10:39 a.m. to 10:50 a.m.)

21 MS. MATTES: We can go back on the record.

22 BY MS. MATTES:

23 Q. Dr. Ratain, before the break, we were in
24 your expert declaration.

25 Can you put that in front of you,

1 please --

2 A. It is.

3 Q. -- if you don't have it.

4 A. I have it.

5 Q. Great. So we were around Paragraph 234.

6 I'd like to talk to you about the proposed
7 modifications to the FOLFIRINOX regimen that you
8 suggest a POSA would make.

9 Can you -- would you agree that there are
10 four modifications that, in your opinion, a POSA
11 would make to the FOLFIRINOX regimen in order to
12 arrive at the claimed invention?

13 MR. SUH: Objection to form.

14 THE WITNESS: Well, you would substitute
15 the liposomal irinotecan for irinotecan, and
16 you'd also obviously have to identify the dose
17 of the liposomal irinotecan.

18 You would drop the 5-FU bolus, and, I
19 mean, the lower oxaliplatin dose is actually
20 part of the FOLFIRINOX regimen, but here in the
21 claim, they're starting with it instead of
22 waiting for the toxicity to develop, as Conroy
23 did, which it pretty much always does,
24 requiring dose reduction.

25 So it's really dropping the 5-FU bolus

1 that others were already doing, being
2 conservative on the oxaliplatin dose. And then
3 the biggest issue was substituting the
4 liposomal irinotecan for irinotecan and
5 figuring out, you know, what dose was an
6 appropriate starting dose in the absence of any
7 UGT1A1 genotype.

8 BY MS. MATTES:

9 Q. Okay. So I think, to summarize, one of
10 the modifications would be to replace irinotecan
11 with liposomal irinotecan, correct?

12 A. Yes.

13 Q. And then after that, you would have to
14 figure out what dose of liposomal irinotecan you
15 would use, correct?

16 A. Yes, for patients for whom you were not
17 doing the genotyping, which is, you know, a pretty
18 iffy proposition.

19 Q. Okay. And then you would -- then the
20 third modification would be to reduce oxaliplatin,
21 correct?

22 A. Yes.

23 Q. And then the fourth modification would be
24 to drop the 5-fluorouracil bolus, correct?

25 A. Correct.

1 Q. In your opinion, is there a particular
2 sequence within which a POSA would make these
3 modifications?

4 A. Well, I think -- look, I think, you know,
5 dropping the 5-FU bolus was pretty straightforward
6 because people didn't think it really added anything
7 to the efficacy. It just added toxicity. That was
8 pretty straightforward.

9 And I think reducing the oxaliplatin dose
10 was pretty, pretty common, and people were doing
11 that in clinical practice anyway.

12 And so, as I said, the most challenging
13 issue was plugging in the liposomal irinotecan in
14 the context of no genotyping.

15 And so that would be the most challenging.
16 And a POSA would have expected that the right dose
17 of irinotecan depended on UGT1A1 genotype, with the
18 most profound effect being in UGT1A1 poor
19 metabolizers, which is about 15 percent of the U.S.
20 population.

21 And so that was the biggest challenge.
22 And if you're doing a Phase 1 trial and you don't do
23 genotyping, obviously, each patient you treat,
24 there's a 15 percent chance that they're a poor
25 metabolizer, and you could run into a lot of

1 toxicity and not figure it out until later that it
2 was because of the genotype.

3 Q. And so, then, I guess in your opinion, the
4 sequence within which a POSA would make these
5 modifications doesn't matter?

6 MR. SUH: Objection to form.

7 THE WITNESS: What do you mean? I'm not
8 sure what you mean, "it doesn't matter."

9 I think you decide what you really care
10 about. You prioritize, and it depends what the
11 POSA is trying to do. If they're -- you know,
12 if a POSA says, look, I'm a big believer in
13 oxaliplatin, I don't want to cut the
14 oxaliplatin dose, and we can drop the 5-FU
15 bolus, no problem, and I want to -- you know, I
16 want to use some irinotecan, but I'm not so
17 concerned about getting the maximal dose in, I
18 just want to be conservative, because, again,
19 you know, it depends on what you're really
20 trying to do.

21 Are you trying to treat a patient? Is the
22 patient frail?

23 So if you just simply say what might a
24 POSA do in clinical practice is one set of
25 questions. What would a POSA do in developing

1 a regimen that's appropriate for FDA approval
2 is a different set of questions.

3 BY MS. MATTES:

4 Q. Okay. And in your opinion, what is the
5 POSA here looking to do?

6 A. Well, I think, legally, my understanding
7 is you have to consider both sets of options. It's
8 clear in this case that the inventors were trying to
9 develop a recipe that would be, you know, eventually
10 suitable for FDA approval. That was the goal of the
11 inventors.

12 But, you know, it's like somebody opens a
13 restaurant and starts marketing their new stew,
14 okay. Their goal was to develop a new restaurant
15 and have some, you know, stew that they could
16 market.

17 Q. You had said that a POSA would be a big --
18 that if a -- sorry. Let me start over again.

19 You had stated in your prior answer that
20 if a POSA was a big believer in oxaliplatin, he or
21 she may not want to cut the oxaliplatin dose.

22 Why would a POSA be a big believer in
23 oxaliplatin?

24 A. Why would somebody think that lots of
25 things? I mean, you know, if you asked me, why does

1 our Secretary of HHS think certain things, I
2 couldn't really give you a good answer.

3 So people think all kinds of things.
4 Everybody has a right to an opinion. And, you know,
5 you might hear somebody say something crazy, like, I
6 had a patient, I cut their oxaliplatin dose, and
7 they didn't do well. I mean, you know, you hear all
8 kinds of crazy stuff from people.

9 Q. Right. A POSA would be trying to balance
10 reducing toxicity but making sure that the patient
11 was still being efficaciously treated, correct?

12 A. The problem is none of these drugs were
13 ever optimized, the dosages. Nobody really knows
14 what -- you know, whether more is better is the real
15 issue.

16 So the standard approach was to try and
17 give the most you can because that was what
18 everybody did. And so, again, oxaliplatin was
19 notorious for the neurotoxicity.

20 So you've got two problems with
21 oxaliplatin. You've got both the fact it increases
22 the short-term toxicity of the other drugs and
23 increases the long-term, and, therefore, you know
24 you're going to have to reduce it anyway, which is
25 why most people would be happy to cut the

1 oxaliplatin and particularly if they wanted to make
2 sure they got enough of the irinotecan in.

3 Q. If a POSA wanted to -- if a POSA wanted to
4 maintain the oxaliplatin dose of FOLFIRINOX but
5 wanted to switch out liposomal irinotecan with
6 irinotecan, what would -- I guess, what would that
7 POSA need to do to feel as though the amount of
8 oxaliplatin they're giving their patient satisfies
9 this need to still reduce toxicity?

10 I don't know if --

11 MR. SUH: Objection.

12 BY MS. MATTES:

13 Q. Let me try to -- yeah, let me rephrase
14 that question.

15 If the POSA's goal was to reduce toxicity,
16 however, they wanted to maintain the same amount --
17 they wanted to maximize the amount of oxaliplatin
18 that their patient was receiving, how would that
19 play into what they -- what decisions they made
20 regarding liposomal irinotecan or the dosing of
21 liposomal irinotecan?

22 MR. SUH: Objection to form.

23 THE WITNESS: They might have to give less
24 of the liposomal irinotecan, okay.

25 A POSA -- but a POSA would know you end up

1 having to cut the dose of the oxaliplatin
2 anyway based on reading Conroy. You know that,
3 you know, patients are getting doses reduced
4 right and left.

5 You also know from the prior art that, you
6 know, such as described in Marsh that
7 practitioners are routinely cutting the dose in
8 older, frail patients just because. They know
9 that the patients are at greater risk for side
10 effects.

11 So it's very common to cut the oxaliplatin
12 dose. But if, hypothetically --
13 hypothetically, oxaliplatin were a brand name
14 product -- and I guess it was at the time, but
15 if, hypothetically, Sanofi were developing
16 liposomal irinotecan, they might approach it
17 differently than Merrimack developing liposomal
18 irinotecan because Sanofi may not want to cut
19 their oxaliplatin dose for commercial reasons.

20 So it really depends on the context.

21 But I think the POSA, the typical POSA
22 would recognize you're going to need to cut the
23 oxaliplatin dose anyway; let's just cut it now
24 so we don't have to think about it.

25

1 BY MS. MATTES:

2 Q. Wouldn't the POSA be concerned with the
3 reduction of oxaliplatin impacting the efficacy of
4 the regimen on the patient? Wouldn't they want to
5 also maximize efficacy?

6 MR. SUH: Objection to form.

7 THE WITNESS: It depends. If the POSA is
8 planning to compare the regimen to FOLFIRINOX
9 and wanted an apples-to-apples comparison, they
10 might.

11 If they're not planning to compare it to
12 FOLFIRINOX, they go, well, what do we care?
13 We're not going to compare it to FOLFIRINOX
14 anyway.

15 BY MS. MATTES:

16 Q. Does Conroy teach reducing oxaliplatin in
17 all patients?

18 A. A huge percentage of patients, not all.

19 Q. It teaches reducing the dose of
20 oxaliplatin in patients who are experiencing certain
21 toxicities, right?

22 A. Well, what it teaches you is that you're
23 going to need to reduce the dose of oxaliplatin in
24 most patients. So that's what it teaches you.

25 So you can -- you know, if you're on the



1 highway and you're following too closely to a car,
2 you know you probably should slow down because you
3 don't want to get into a crash. You don't need to
4 wait for the crash to say, "I should have slowed
5 down."

6 So it's really anticipating the problem
7 and preventing it by cutting the dose. That's what
8 Conroy teaches. It teaches a POSA who understands
9 that the oxaliplatin dose isn't critical.

10 Q. And so Conroy teaches reducing the
11 starting dose of oxaliplatin in patients once they
12 experience a certain toxicity, right?

13 A. Conroy teaches, explicitly teaches
14 reducing the dose after toxicity, implicitly teaches
15 reducing the dose before toxicity.

16 Q. Where does -- how does Conroy implicitly
17 teach that?

18 A. By telling you the percentage of people
19 that had dose reductions, the dose intensity, those
20 kinds of data; telling you that the population they
21 studied, which is a very constrained population, so
22 that if you want to study a less fit population, a
23 POSA would understand you need to reduce the doses.

24 Q. So you're referencing the fact that the
25 dose intensity for oxaliplatin in Conroy was not

1 100 percent, correct?

2 A. It wasn't anywhere close to 100 percent,
3 yeah.

4 Q. It was 78 percent; is that right?

5 A. I'd have to look at it to answer that
6 question. I can say that sounds about right.

7 (Exhibit 1003 was marked for
8 identification.)

9 BY MS. MATTES:

10 Q. I believe Conroy is Exhibit 1003, if you
11 want to take that out.

12 A. Yes. So in answer to your question, so it
13 was -- the oxaliplatin median relative dose
14 intensity was 78 percent. That's median. That
15 means half the patients had a dose intensity of less
16 than 78 percent. And each dose, when you reduce the
17 dose of oxaliplatin, according to protocol, that's a
18 30 percent dose reduction.

19 And so if you've got -- if you were to get
20 half your doses at the reduced dose, you would have
21 an 85 percent dose intensity.

22 So it's basically telling you less than
23 half the doses administered were a full dose.

24 Q. The 78 percent dose, median dose intensity
25 represents the dose intensity across all cycles of

1 the treatment, correct?

2 A. Right.

3 Q. Right. It's not just the first? It's not
4 for the first cycle of the treatment, correct?

5 A. No. The first cycle, this highly selected
6 group of patients, okay, who were younger than 76
7 and had a performance status zero of one, no cardiac
8 ischemia, and nearly normal bilirubin levels were
9 not reduced the first cycle. But more than half of
10 their cycles, they were dose-reduced.

11 Q. So for the first starting cycle, all the
12 patients reported in the trial that Conroy reports
13 on were dosed with 85 milligrams per meter squared
14 of oxaliplatin, correct?

15 A. Yes.

16 Q. And that's per the Conroy protocol, right?

17 A. That is per the Conroy protocol, yes, for
18 that set of patients.

19 Q. Right. And so then after that first cycle
20 of treatment, there was a proportion of patients who
21 received a reduced dose of oxaliplatin for various
22 reasons, correct?

23 A. Yes. All we know is that more than half
24 of the cycles were administered at a dose of
25 60 milligrams per meter squared or less.



1 Q. Right. And you also know that some
2 patients received the full dose of 85 milligrams per
3 meter squared as well in subsequent cycles after the
4 first cycle, correct?

5 A. Well, we don't know that. We actually
6 don't know that. It's never -- I don't think it's
7 explicitly stated in the prior art that any patient,
8 you know, didn't -- were not dose-reduced.

9 Q. Okay. So the 78 percent doesn't tell you
10 exactly the number of patients that were
11 dose-reduced, correct?

12 A. It does not.

13 Q. Okay.

14 A. It only teaches you that dose reduction is
15 likely. And Conroy also teaches you if you want to
16 administer FOLFIRINOX to a group of patients, a
17 broader group of patients than those described here,
18 that you have -- that you can't rely on the doses
19 here, basically. So --

20 Q. Where does it say that?

21 A. The last paragraph of the paper. It
22 implies that. That's what a POSA --

23 Q. That's on Page --

24 A. Yeah, Page 1824, a POSA would understand
25 from the last paragraph that the FOLFIRINOX regimen

1 is only an option for the patients that are
2 described in that paragraph.

3 Q. And when it uses the term "FOLFIRINOX"
4 here, it's referring to the regimen that includes
5 the 85 milligram per meter squared oxaliplatin dose,
6 correct?

7 A. Yes.

8 Q. Okay. When papers refer to the FOLFIRINOX
9 regimen, a POSA would understand that the paper is
10 referring to the regimen that includes the
11 85 milligrams per meter squared oxaliplatin starting
12 dose, right?

13 A. Yes.

14 MR. SUH: Objection.

15 BY MS. MATTES:

16 Q. Okay. If the motivation for a POSA was to
17 reduce toxicity, and if replacing the irinotecan
18 with liposomal irinotecan achieved, achieved that
19 goal --

20 MR. SUH: Objection to form.

21 BY MS. MATTES:

22 Q. -- would a POSA -- would a POSA still make
23 further modifications?

24 A. All right. So what's the hypothetical
25 you're asking me?

1 Q. If a POSA, if their goal was to reduce
2 toxicity of FOLFIRINOX, and the replacement of
3 irinotecan with liposomal irinotecan achieved that
4 goal, would there be a motivation to make any
5 further modifications to the regimen?

6 MR. SUH: Objection to form.

7 THE WITNESS: It depends what group of
8 patients you wanted to treat.

9 BY MS. MATTES:

10 Q. How so?

11 A. Well, if you want to treat a broader group
12 of patients than was treated in Conroy, yes, you
13 would have to make sure it was significantly safer,
14 and you'd have to make sure that it was safe in a
15 wider range of patients.

16 So it would -- it would depend.

17 So, yes, a POSA would want to know what
18 the options were, and, you know, again, you know,
19 what's a good regimen for somebody, you know, who is
20 older, who has a performance status of 2, for
21 example, or maybe has a biliary stent in.

22 These are all questions that arose or that
23 would arise based on reading Conroy because you
24 don't know.

25 Q. So you don't know until you make the



1 modification whether -- a POSA would -- let me start
2 over.

3 A POSA would not know until they make the
4 modification whether or not they would be able to
5 achieve their goal, correct?

6 A. Well, and, again, the goal, what's the
7 goal? If the goal is to make it -- to make it less
8 toxic, well, you can always make it less toxic by
9 reducing a dose. That's easy.

10 So it depends what the goal is. If you
11 really want to say what's the optimal regimen, the
12 truly optimal regimen, you have to do what's never
13 been done, which is a randomized, dose-ranging trial
14 in patients, you know, in a consistent group of
15 people, and control for UGT1A1 genotype and ask the
16 question, "What's the best dose?" And that's not a
17 simple experiment to do.

18 So at the end of the day, you can do what
19 was, you know, sort of this routine experimentation
20 where you, like cooking, you can add a little of
21 this and add a little of this and subtract a little
22 of this, and that's what was -- that's pretty much
23 oncology clinical trials.

24 Q. And a POSA wouldn't know what the result
25 of that experimentation would be unless they

1 experimented in the first place, correct?

2 A. It depends if they were trying to find an
3 optimal regimen or a regimen that was simply
4 effective, okay.

5 If they wanted to find a regimen that was
6 simply effective, it's pretty, pretty simple because
7 you know that 5-FU-leucovorin are effective,
8 5-FU-leucovorin plus oxaliplatin are effective. You
9 don't even need any liposomal irinotecan if you just
10 want an effective regimen.

11 If you want a regimen that's suitable for
12 FDA approval, you have to beat something. You have
13 to show superiority generally in a randomized
14 clinical trial, and, therefore, you're trying to set
15 a higher bar for yourself. You don't want to fail
16 in your clinical trial, so you're going to push it a
17 little further to try and find, you know, the best
18 regimen you can within financial constraints.

19 Q. Okay. So would a POSA have had any
20 understanding as to whether replacing 180 milligrams
21 per meter squared of irinotecan with 60 milligrams
22 meter squared of liposomal irinotecan would have
23 achieved the goal of reducing toxicity as of
24 August 2015?

25 MR. SUH: Objection to form.

1 THE WITNESS: They would have to do the
2 simple experiment of administering that.

3 BY MS. MATTES:

4 Q. So they would have to test it, correct?

5 A. Yes. That's the only way you can know
6 with certainty. I mean, you could cut the -- you
7 know, there's two ways of doing this.

8 One, you start with zero or some low dose
9 and work your way up, and the other way is you start
10 at a dose that might work and work your way down.

11 They're both, both reasonable approaches
12 that a POSA would use.

13 Q. If a POSA first modified the FOLFIRINOX
14 regimen by lowering the dose of oxaliplatin and that
15 achieved the goal of reducing toxicity, would there
16 be a reason for a POSA to further modify that
17 regimen?

18 MR. SUH: Objection to form.

19 THE WITNESS: Again, it depends on the
20 goal. You keep -- we keep talking about the
21 goal.

22 The goal of the claims is to treat
23 pancreatic cancer. It's not to get FDA
24 approval. If all you want to do is treat
25 pancreatic cancer, it's easy.



1 If you're trying to get FDA approval,
2 which is -- and so that's really what it comes
3 down to is, are you asking me what a POSA would
4 do if they were working for a company or, you
5 know, contracted to a company to help the
6 company get FDA approval. Or are you asking me
7 what a POSA would do if all they want to do is
8 treat pancreatic cancer but use -- use
9 liposomal irinotecan instead of irinotecan. I
10 mean, or if they just want to develop a, you
11 know, less toxic FOLFIRINOX regimen and still
12 treat pancreatic cancer.

13 So I'm a little bit confused by your
14 question.

15 BY MS. MATTES:

16 Q. I guess I'm trying to figure out where
17 you're coming from.

18 So in your opinion, what is a POSA trying
19 to do here?

20 MR. SUH: Objection to form.

21 THE WITNESS: It depends what the POSA's
22 goal is. If the goal -- the claimed method is
23 not a method to treat pancreatic cancer with an
24 FDA-approved drug, okay.

25 It's not a method to treat pancreatic

1 cancer and to get Onivyde approved by FDA.
2 It's a method to simply treat pancreatic
3 cancer, okay.

4 And so that's really very easy. One can
5 easily treat pancreatic cancer, and it's pretty
6 straightforward to say, well, we will cut the
7 oxaliplatin dose because we know that that has
8 to be cut anyway in many patients. We will
9 drop the 5-FU bolus because that was a common
10 modification, and we will give a dose of
11 liposomal irinotecan that the prior art teaches
12 is effective, and that's it. And as long as it
13 doesn't kill people, it's an effective
14 treatment for pancreatic cancer.

15 BY MS. MATTES:

16 Q. When you say "effective," what do you
17 mean? In your opinion, what does it mean to be
18 effective in treating pancreatic cancer?

19 MR. SUH: Objection to form.

20 THE WITNESS: It means to treat one or
21 more symptoms of the disease and/or to reduce
22 the size of the tumor or reduce the rate of
23 growth of the tumor.

24 BY MS. MATTES:

25 Q. And that's something that's easy to do?



1 MR. SUH: Objection.

2 THE WITNESS: It's easy to do with drugs
3 that are known to be active in patients who
4 have not had any prior chemotherapy, yes.

5 BY MS. MATTES:

6 Q. Do you consider prolonging life or life
7 expect -- excuse me.

8 Do you consider prolonging life expectancy
9 to also be part of an effective pancreatic cancer
10 treatment?

11 A. Well, sure. But that's -- I've never seen
12 that achieved without one of the other things I
13 mentioned.

14 Q. If a POSA's goal was to achieve a
15 treatment that provides more than a de minimis
16 benefit, and lowering the dose of oxaliplatin in
17 FOLFIRINOX achieved that goal, would there be a
18 further reason to modify the regimen?

19 MR. SUH: Objection to form.

20 THE WITNESS: There are -- there are many
21 reasons to modify a regimen because you
22 would -- you would -- you know, if you just
23 want a treatment, then, you know, FOLFIRINOX is
24 a safe and effective treatment for pancreatic
25 cancer.

1 The goal -- you know, a POSA is always
2 motivated to modify a safe and effective
3 treatment to make it better because it's not as
4 safe as it could be and it's not as effective
5 as it could be.

6 So we've gone through this from the
7 beginning. You can always improve something
8 even better, okay. We have planes that can fly
9 us across oceans. Why would anybody be making
10 supersonic aircraft now? Because it can be
11 better, spend less time in the air.

12 So there's always a reason to make things
13 better, and there's always concern about trying
14 to make things better.

15 BY MS. MATTES:

16 Q. Let's go to -- sorry. I guess one more
17 question before we switch gears.

18 So then it's your opinion that a POSA
19 would continue to modify treatment regimens even if
20 they achieved their goal?

21 MR. SUH: Objection to form.

22 THE WITNESS: The goal has not been
23 achieved yet today. We don't have a curative
24 regimen for metastatic pancreatic cancer, and
25 people continue to develop new regimens for



1 metastatic pancreatic cancer.

2 BY MS. MATTES:

3 Q. If the goal were to achieve a treatment
4 that provides more than a de minimis benefit, it's
5 your opinion that a POSA would continue to modify
6 treatment even if that goal was achieved?

7 A. Yes.

8 Q. All right. Let's go to Paragraph 244 of
9 your report. Let me know when you're there.

10 A. I'm here. I'm sorry.

11 (Exhibit 1005 was marked for
12 identification.)

13 BY MS. MATTES:

14 Q. Okay. I think you should probably also
15 have Exhibit 1005 in hand, which is the Mahaseth
16 reference, in case needed. You may have pulled that
17 already previously.

18 A. No, I've got it.

19 Q. Okay. All right, great.

20 And so here you talk about the
21 modification of removing the 5-fluorouracil dose,
22 correct?

23 A. The bolus.

24 Q. Excuse me, correct. So here you're
25 discussing the removal of the 5-fluorouracil bolus

1 dose, correct?

2 A. Yes.

3 Q. And you state that a POSA would have known
4 to make that modification in order to improve the
5 toxicity profile, correct?

6 A. It was one known -- one known
7 modification.

8 Q. And you rely on Mahaseth as teaching that
9 modification, right?

10 A. As well as papers that -- other
11 publications that have cited this paper.

12 Q. Okay. Fair enough.

13 If you take the Mahaseth paper and have
14 that in front of you as well.

15 The modified FOLFIRINOX regimen that
16 Mahaseth teaches includes a starting dose of
17 oxaliplatin at 85 milligrams per meter squared,
18 correct?

19 A. That's what they said.

20 Q. The -- is the only modification Mahaseth
21 made to the FOLFIRINOX regimen the removal of the
22 5-fluorouracil bolus dose?

23 A. Yeah, I don't know whether the patients
24 they treated here might have been somewhat different
25 in some way. There's some earlier-stage patients,

1 for example, Stage 2 and 3 patients, that would not
2 have been treated in Conroy.

3 So this was also a retrospective analysis.
4 So what -- basically, this reports on an experience
5 at Emory University where the group there just made
6 the modification before they approved anything.
7 They just said, we're going to get rid of the 5-FU
8 bolus. And then, later, it was decided, well, we
9 should pull all these patients that we did this in
10 and report how they did.

11 But the POSA did this outside of a
12 clinical trial because they thought it was medically
13 appropriate, and so they just did --

14 Q. And that's why you --

15 A. Yes.

16 Q. I didn't mean to cut you off, if you're
17 not finished with your answer.

18 A. Well, I said they just did it. Starting
19 in, looks like, June 2010, they just started doing
20 it.

21 Q. Okay. And what they started to do was
22 remove the 5-fluorouracil bolus dose, correct?

23 A. That's what they said, yes.

24 Q. Right. And if you go to Page -- it's 2 of
25 the exhibit but of the article it's 1312 -- I don't

1 know which numbering you prefer -- where it says
2 "Chemotherapy," right under there, it explains the
3 regimen, the modified FOLFIRINOX regimen that
4 Mahaseth used as part of their retrospective study,
5 correct?

6 A. Well, it's not the regimen they used.
7 It's the regimen that was -- it was patients who
8 received this regimen were included in this report.

9 Q. And the regimen included oxaliplatin at
10 85 milligrams per meter squared, correct?

11 A. Well, for at least one -- you know, the
12 population reported here is 60 patients who received
13 at least one dose of modified FOLFIRINOX. That's
14 what they say, as I said, includes Stage 2 and 3
15 patients as well as Stage 4 patients.

16 Q. And are you reading that under "Patient
17 Characteristics," where it said -- where it says,
18 "60 consecutive patients with PC were treated with
19 at least one dose of modified FOLFIRINOX"?

20 A. Yes.

21 Q. Okay. And when it says here "modified
22 FOLFIRINOX," it's referring to the regimen described
23 under the Chemotherapy section that we were just
24 looking at, correct?

25 A. Yes.



1 Q. Right. And that's the regimen with
2 85 milligrams per meter squared of oxaliplatin,
3 right?

4 A. That's correct.

5 Q. Great. And the modification that was made
6 to the FOLFIRINOX regimen was that the patients here
7 did not receive the bolus 5-fluorouracil, correct?

8 A. That's right. You know, I just want to
9 check one thing in Conroy.

10 So in contrast to Conroy, they've made one
11 other change here. They also administered
12 pegfilgrastim to all patients in Mahaseth.

13 Q. What is -- I'm not going to even try to
14 pronounce the word. What is pegfilgrastim?

15 A. Its brand name is Neulasta,
16 N-e-u-l-a-s-t-a. You might have heard of that.
17 It's a PEGylated form of filgrastim granulocyte
18 colony-stimulating factor. And they did this
19 because they were still concerned about low blood
20 counts, neutropenia. And so they did this
21 preemptively as well.

22 So this was not done in Conroy. Conroy
23 makes a point of explicitly saying they didn't do
24 that.

25 Q. So in addition to removing the

1 5-fluorouracil bolus dose, Mahaseth added another
2 component called -- let me find the name so I don't
3 mispronounce it -- pegfilgrastim, correct?

4 A. Yes.

5 Q. Okay.

6 MR. SUH: Counsel, is this a good time for
7 another break? We've gone for another hour.

8 MS. MATTES: If you don't mind, let me
9 just finish my questions with Mahaseth, and
10 then we can take a break --

11 MR. SUH: Sure.

12 MS. MATTES: -- if that works.

13 Thank you.

14 BY MS. MATTES:

15 Q. You state in Paragraph 244 of your expert
16 declaration that the Mahaseth modified regimen was
17 well-tolerated and had an improved safety profile of
18 the original FOLFIRINOX regimen, correct?

19 A. Yes.

20 Q. And that was with respect to neutropenia,
21 fatigue, and vomiting; is that right?

22 A. Correct.

23 Q. And you stated that the Mahaseth modified
24 FOLFIRINOX regimen also maintained the FOLFIRINOX's
25 overall efficacy, right?



1 A. Well, the modified regimen is an effective
2 regimen, that's for sure. You can't say that it's
3 the same, better, or worse than FOLFIRINOX because
4 the patients are different, it was retrospective,
5 and you just can't draw that conclusion. All you
6 can say, it's effective treatment.

7 Q. The Mahaseth modified FOLFIRINOX regimen
8 was an effective treatment for pancreatic cancer?

9 A. Yes.

10 Q. And so it would be your opinion that the
11 Mahaseth modified FOLFIRINOX regimen achieved its
12 goal of improving the toxicity profile of the
13 FOLFIRINOX regimen, correct?

14 A. That's what the -- that's what the paper
15 teaches, and, you know, you can't draw definitive
16 conclusions, but it's certainly an effective
17 treatment.

18 Q. And it would be a safe treatment, too,
19 correct?

20 A. I'm sorry?

21 Q. And it would be a well-tolerated or safe
22 treatment as well, correct?

23 A. Yes. Yes, it was, you know, safer than
24 the treatment administered in Conroy.

25 MS. MATTES: Okay. I think we can take

1 our break now.

2 MR. SUH: Thank you.

3 (Whereupon, a recess was taken
4 from 11:41 a.m. to 11:53 a.m.)

5 MS. MATTES: Okay. We're back on the
6 record.

7 BY MS. MATTES:

8 Q. Welcome back, Dr. Ratain.

9 I'd like you to turn to Paragraph 242 of
10 your expert report. I just have a couple of
11 questions.

12 In this paragraph, you state -- it's
13 towards the bottom of the page, "A POSA would have
14 been motivated to select a dose that had already
15 been used or tested."

16 And then one of the citations in the
17 parenthetical says, "See also Section VIII.H, also
18 disclosing a 60-milligram per meter squared dose of
19 oxaliplatin."

20 Do you see that?

21 A. Yes.

22 Q. So Section VIII.H, if you look at your
23 Table of Contents, refers to a publication you
24 entitled Masi.

25 Do you see that?

1 A. Yes.

2 (Exhibit 1012 was marked for
3 identification.)

4 BY MS. MATTES:

5 Q. Okay. And then if your attorneys don't
6 mind passing you Exhibit 1012, which I believe
7 should be the Masi publication.

8 Let me know when you have Masi in front of
9 you.

10 A. I have Masi, but then I want to read
11 VIII.H. Oh, I see the problem.

12 Let me just refresh.

13 Yeah, obviously, this is the wrong
14 reference for that statement.

15 Q. Okay. I just wanted to make sure I wasn't
16 missing something in Masi because I didn't see you
17 discuss anywhere in your report that Masi taught a
18 dose of 60 milligrams per meter squared of
19 oxaliplatin.

20 A. No, you are correct.

21 Q. Okay.

22 A. There are other references that do, but
23 not that.

24 Q. It's not your -- right.

25 So it's not your opinion that Masi teaches

1 a dose of 60 milligrams per meter squared of
2 oxaliplatin, correct?

3 A. Correct.

4 Q. Okay. In the next sentence, you reference
5 Cantore.

6 Do you see that?

7 A. Yes.

8 Q. So you state, "A POSA would have
9 understood that other art, like Cantore, showed or
10 suggested that these lower dose regimens, including
11 a 60-milligram per meter squared dose of oxaliplatin
12 along with 60 milligrams per meter squared
13 irinotecan, were found to be safe and effective in
14 metastatic pancreatic cancer patients," right?

15 A. Yes.

16 Q. And I believe Cantore is Exhibit 1009.
17 I'm not sure if you have that in front of you from
18 before.

19 A. If we pulled it up before, it's still in
20 front of me.

21 Here it is.

22 Q. Okay, perfect. Cantore was published
23 prior to the development of the FOLFIRINOX regimen,
24 correct?

25 A. Yes.

1 Q. And Cantore concluded that future studies
2 should try higher doses of irinotecan and
3 oxaliplatin for patients with advanced pancreatic
4 cancer, correct?

5 MR. SUH: Objection to form.

6 THE WITNESS: I'm not sure if it says
7 that.

8 BY MS. MATTES:

9 Q. If you go to the last page, the very last
10 sentence, it states, "Future studies should try
11 higher doses of irinotecan and oxaliplatin in such
12 patients."

13 Correct?

14 A. That's a hypothesis. But the point is
15 this regimen is effective, and if you're trying
16 to -- you know, that's one possible modification,
17 and that modification was used by Conroy. But
18 there's no question that a POSA would understand
19 from Cantore that a dose of 60 milligrams per meter
20 squared is effective.

21 So if the simple goal is let's come up
22 with an effective regimen, it can be part of an
23 effective regimen. It doesn't mean that it's the
24 optimal dose because we don't know what the optimal
25 dose is of any of these regimens.

1 Q. After conducting this study, Cantore
2 stated that they should try higher doses of
3 irinotecan and oxaliplatin, though, correct?

4 MR. SUH: Objection to form.

5 THE WITNESS: Let me make it -- you know,
6 it would be obvious to try a higher dose of
7 irinotecan and oxaliplatin based on simply this
8 reference that, you know, just a suggestion
9 that -- you know, Cantore also notes in the
10 discussion on page -- on the preceding page,
11 first full paragraph, right-hand column, the
12 last two sentences, they say, "In light of the
13 excellent tolerability of this regimen, dosages
14 could possibly be increased in future studies
15 in an effort to boost response."

16 But then they add about experience in
17 colorectal cancer with oxaliplatin 85-milligram
18 per meter squared and irinotecan 80 per meter
19 squared, and often G-CFS support, 31 percent of
20 patients required dose reductions because of
21 toxicity.

22 So they're basically saying a higher dose
23 might be better, but the higher dose is
24 probably going to require dose reduction in
25 many, if not most patients.

1 BY MS. MATTES:

2 Q. What type of study is the Cantore
3 reference?

4 A. I'm sorry. What do you mean by "what type
5 of study"?

6 Q. Is this -- I guess is this a Phase 2 trial
7 or a Phase 1 trial? What kind of trial is this?

8 MR. SUH: Objection to form.

9 THE WITNESS: I would describe this as a
10 Phase 2 trial.

11 BY MS. MATTES:

12 Q. Is this a single-arm trial or a two-arm
13 trial?

14 A. It's a single-arm trial.

15 Q. And does it have a control group?

16 A. The only control group would be historical
17 controls.

18 Q. In your opinion, would this type of trial
19 provide a POSA with a strong inference that the
20 combination of 60 milligrams per meter squared of
21 oxaliplatin and 60 milligrams per meter squared of
22 irinotecan would be a safe and effective treatment?

23 MR. SUH: Objection to form.

24 THE WITNESS: It is a safe and effective
25 treatment. It doesn't provide any -- a POSA

1 with any understanding that this is the best
2 treatment or that this would be, you know,
3 amenable to a -- it would succeed in a Phase 3
4 trial or could garner FDA approval. But
5 there's no question it's a safe and effective
6 treatment.

7 BY MS. MATTES:

8 Q. I see what you're saying.

9 So it would not -- it would not provide a
10 POSA with an understanding as to whether or not this
11 regimen would succeed in a Phase 3 trial, correct?

12 A. That's correct.

13 Q. Okay. You can put that to the side.

14 Okay. So let's go back to Paragraph 235
15 of your expert report where you're discussing the
16 modification of replacing irinotecan with liposomal
17 irinotecan, and let me know when you're there.

18 A. I'm here. Do you want me to read the
19 paragraph, or do you want to ask me a question?

20 Q. No, I have questions.

21 Is it your opinion that a POSA would have
22 been motivated to replace irinotecan with liposomal
23 irinotecan because of liposomal irinotecan's
24 potential superior -- superiority over irinotecan?

25 A. Well, I think that was one potential

1 approach to trying to improve the efficacy of
2 Conroy.

3 Q. Is it your opinion that as of August 2015,
4 a person of skill in the art would have known that
5 liposomal irinotecan was superior to irinotecan?

6 A. Well, the prior art disclosed evidence
7 that -- teaching that it was. Now, "know" is a --
8 I'm not sure what you mean by "know." They would
9 have understood that there's prior art that teaches
10 that.

11 Would they be certain that that -- that
12 there's -- that those prior art statements are
13 truthful? Well, no. But that doesn't mean that the
14 prior art didn't teach that.

15 Q. So a POSA, as of August 2015, would have
16 had an understanding that liposomal irinotecan could
17 have been superior to irinotecan; is that right?

18 A. They would see the evidence that would
19 suggest that it is better but knowing that at the
20 end of the day you won't know until you do the
21 comparative clinical trials, which, as I testified
22 to earlier, have not yet been done, showing, indeed,
23 that it is superior to irinotecan.

24 Q. Okay. And when you -- you used the word
25 "superiority" in your declaration.



1 And when you use that word with respect to
2 liposomal irinotecan, you're referencing the
3 purported superiority of the compound itself and
4 not -- and not in combination with other agents,
5 correct?

6 A. I'd have to take a look at the Bayever --
7 not the '552, but the other patent, because there's
8 a lot that's taught and disclosed in that patent
9 that I believe talks about the combination with 5-FU
10 and leucovorin.

11 Q. Okay. I guess maybe the easier question
12 would be, when you talk about the superiority of
13 liposomal irinotecan, what exactly are you referring
14 to?

15 A. I'm referring to the preclinical
16 pharmacology that suggests that liposomal irinotecan
17 is both more effective and safer than irinotecan.

18 Q. And when you talk about the preclinical
19 pharmacology, which reference are you relying on?
20 Bayever?

21 A. Primarily Bayever. I can't remember
22 whether there may be some statements to that effect
23 in some of the other, you know, such as Saif or in
24 Ko as to what they said, but primarily Bayever.

25 Q. And Bayever is Exhibit 1006, if you want

1 to take that out.

2 And then can you direct me to which
3 studies or what portions of Bayever you're relying
4 on for your opinion that a POSA would -- a POSA may
5 consider liposomal irinotecan to be superior to
6 irinotecan?

7 A. Well, Figure 1 is pretty compelling. It
8 shows a pancreatic tumor model in which irinotecan
9 was ineffective and liposomal irinotecan was
10 effective.

11 Figure 2 shows greater accumulation of the
12 active metabolite in tumors with the liposomal drug.

13 Those are the two data points that really
14 speak to the potential for great efficacy.

15 Q. Okay. And as you said before, those are
16 both preclinical studies, correct?

17 A. Those are preclinical studies, yes.

18 Q. And are these tumor models in animals? In
19 mice?

20 A. Yes.

21 Q. Okay. And so one of the possible superior
22 properties is improved efficacy.

23 Is there anything else that you're taking
24 into account besides that for your conclusion that
25 it could be superior?

1 A. This I'm looking at. I thought there were
2 some statements also about safety somewhere in here.

3 I don't see any discussion, any explicit
4 discussion of safety in Bayever suggesting that it's
5 safer, you know. There's data in here but no
6 explicit statement that they feel it's safer, just
7 more effective.

8 Q. Okay. If you'd go to Page 20 of Bayever,
9 which in the exhibit numbering it's Page 21 of 66,
10 just so that we're on the same page.

11 A. So 20 of the exhibit, you said?

12 Q. Yes. It's really Example 5. I just don't
13 want to confuse the numbering.

14 A. Okay. All right. All right. I'm in --

15 Q. Right. The document says Page 20, but the
16 stamp at the bottom says 21 of 66, so it's
17 Example 5.

18 A. Okay.

19 Q. Example 5 is a Phase 1 clinical study,
20 correct?

21 A. Yes.

22 Q. And so is Example 6?

23 A. Yes.

24 Q. Okay. And then Example 7 is a -- is a
25 protocol for a planned Phase 3 trial, correct?

1 A. Yes.

2 Q. Okay. So Bayever doesn't include any
3 Phase 2 trial results, right?

4 A. No. Their Phase 1, in combination with
5 FU-leucovorin, was kind of a Phase 1-Phase 2 study.
6 I don't know what you would call it. I mean, I'd
7 have to look at the protocol.

8 They note that there were 5 subjects with
9 pancreatic cancer out of the 16. They note that
10 there was a gastric cancer with a response and a
11 breast cancer with a response.

12 So it's really a pretty broad group of
13 patients.

14 Q. Would a POSA, based on the Phase 1 trial
15 results, be able to make an inference about the
16 safety or efficacy of liposomal irinotecan?

17 A. Well, they would know it's a safe and
18 effective treatment, sure. They wouldn't know that
19 it's going to get them FDA approval. It depends
20 what the control arm is.

21 Q. How would they know that it would be a
22 safe treatment?

23 A. It is safe. It's safe. This describes
24 the safety. In absolute sense, it's safe.

25 Is it the safest possible treatment? No.

1 Is it the best possible treatment? No. But that's
2 not the objective of, you know, of the claims. The
3 claim is to find a safe and effective treatment.

4 So this alone is a safe and effective
5 treatment.

6 Q. Does Bayever discuss dose equivalency
7 between liposomal irinotecan and irinotecan?

8 A. What do you mean by "dose equivalency"?

9 Q. If you have a dose of 180 milligrams per
10 meter squared of irinotecan, how -- do you know how
11 much liposomal irinotecan to give to achieve the
12 same results?

13 MR. SUH: Objection to form.

14 THE WITNESS: What do you mean by "the
15 same results"?

16 BY MS. MATTES:

17 Q. To achieve the same level of safety and
18 efficacy.

19 A. Well, the goal of substituting liposomal
20 irinotecan is to increase efficacy.

21 Q. Is that your answer?

22 A. Well, that would be the motivation.

23 Q. But how would you know how much liposomal
24 irinotecan to give to achieve the same results or
25 better results of irinotecan?

1 A. Same compared to what?

2 Q. If you have a treatment regimen that doses
3 a patient with 180 milligrams per meter squared of
4 irinotecan and you want to replace that with
5 liposomal irinotecan, how do you know how much
6 liposomal irinotecan to provide to that patient in
7 order to achieve the same level of safety and
8 efficacy?

9 A. You can never prove you have the same
10 level of safety and efficacy, so I can't answer that
11 question.

12 Q. Okay. In Example 6 of Bayever, it
13 concluded that the maximum tolerated dose for
14 liposomal irinotecan was 80 milligrams per meter
15 squared, correct?

16 A. That's what the specification says.

17 Q. Okay. And that was the dose that they
18 carried into -- into one of the arms of their
19 Phase 3 trial in Example 7, correct?

20 A. Well, in Example 7, they now say that
21 they're only going to give that dose to patients
22 that are UGT1A1 -- that are not UGT1A1*28
23 homozygotes. So that's what they're saying there.

24 I don't know what they did in Example 6
25 related to UGT1A1 status. I mean, UGT1A1 status has

1 a huge effect on the tolerability of irinotecan.
2 And so a POSA would understand that and would assume
3 it would have a huge effect on the tolerability of
4 liposomal irinotecan.

5 So it's a little difficult to interpret
6 the dosages exactly.

7 Q. For patients who are homozygous for
8 UGT1A1*28, that arm suggests giving a reduced dose
9 of 60 milligrams per meter squared, correct?

10 A. That's right.

11 Q. Right. And then if no toxicity is
12 observed, then it recommends increasing the dose of
13 liposomal irinotecan, correct?

14 A. Yes, it says did not experience any
15 drug-related toxicity. That seems virtually unheard
16 of.

17 Q. That's what the protocol here suggests,
18 though, correct?

19 A. Yes, but a POSA would understand that
20 because you're giving it with 5-FU-leucovorin,
21 you're going to have some toxicity, even if it
22 didn't have any toxicity by itself.

23 Q. Right. But the protocol here does state
24 that if there is no toxicity, the dose may be
25 increased to 80 milligrams per meter squared, right?

1 A. That's what it says.

2 Q. Okay. Do you know prior -- actually,
3 never mind.

4 You can put Bayever to the side. And
5 let's pull out Exhibit 1008, which is Ko.

6 (Exhibit 1008 was marked for
7 identification.)

8 THE WITNESS: Okay. I have that.

9 BY MS. MATTES:

10 Q. Okay. And you rely on Ko in support of
11 your proposed modification of replacing liposomal
12 irinotecan -- excuse me, replacing irinotecan with
13 liposomal irinotecan, correct?

14 A. I would say I don't need to rely on it,
15 but it's consistent with my opinions.

16 Q. And Ko is a Phase 2 study; is that right?

17 A. Yes.

18 Q. And it's a single-arm trial that was not
19 randomized; is that right?

20 A. That's right.

21 Q. Okay. And Ko studied liposomal irinotecan
22 as a monotherapy, correct?

23 A. Yes.

24 Q. Okay. And it used a dose of liposomal
25 irinotecan of 120 milligrams per meter squared; is



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1 that right?

2 A. That was the initial dose, and then they
3 reduced it to 100 milligrams per meter squared.

4 Q. When was it reduced to 100 milligrams per
5 meter squared?

6 A. It said "subsequently amended during the
7 second stage of the study."

8 Q. Okay. And did Ko allow for dose
9 escalation up to 150 milligrams per meter squared of
10 liposomal irinotecan if no toxicities were observed?

11 A. It did.

12 Q. And Ko did not compare liposomal
13 irinotecan to irinotecan in its study, correct? It
14 was just a one-arm study?

15 A. That's right.

16 Q. If you go to the conclusion of Ko at the
17 end on Page 924, and let me know when you're there.
18 It's the last paragraph.

19 A. I'm there.

20 Q. Okay. And the very last sentence states,
21 "Moreover, given the emergence of FOLFIRINOX as a
22 front-line standard in patients with good
23 performance status, the utility of PEP02 in
24 irinotecan-pretreated patients, alone or in
25 combination with gemcitabine, also merits further

1 investigation."

2 Do you see that?

3 A. I do.

4 Q. So a POSA, based on Ko, would be motivated
5 to pursue a combination therapy of liposomal
6 irinotecan with gemcitabine, correct, as a
7 second-line therapy?

8 MR. SUH: Objection to form.

9 THE WITNESS: Well, that's what it says.
10 I don't understand why the authors thought that
11 PEP02 liposomal irinotecan would be effective
12 in patients who already had prior FOLFIRINOX.

13 So I don't understand what they're saying
14 there.

15 BY MS. MATTES:

16 Q. But you agree that that's what they are
17 saying, that a -- that their recommendation is to
18 try liposomal irinotecan in combination with
19 gemcitabine as a second-line therapy, correct?

20 MR. SUH: Objection to form.

21 THE WITNESS: Well, I understand that
22 that's what they're saying, but a POSA wouldn't
23 quite -- would be scratching their head saying,
24 "That doesn't make sense to me."

25



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1 BY MS. MATTES:

2 Q. And why do you say that?

3 A. Well, because generally you wouldn't
4 retreat a patient with pancreatic cancer who has
5 just failed an irinotecan-based regimen with
6 irinotecan because -- you know, and I'm not aware of
7 any evidence the combination gemcitabine and
8 irinotecan is effective in patients that have
9 already failed irinotecan.

10 I might be wrong, but there's no
11 references in here to support it, and I actually
12 have never looked at that because it's not something
13 that I would ever have considered.

14 Q. Right. And then why do you rely on Ko,
15 then, for your opinion here?

16 A. I rely on Ko for the previous sentence,
17 "Additional studies may explore this drug's
18 potential role in the first-line setting as part of
19 combination regimens for advanced pancreatic
20 cancer."

21 And that's because Ko discloses the fact
22 that liposomal irinotecan is an effective treatment
23 for pancreatic cancer.

24 Q. So you're relying on Ko's general
25 statement to combination regimens for advanced

1 pancreatic cancer, correct?

2 A. Yes, and for the fact that Ko demonstrates
3 that the drug works as a single agent in advanced
4 pancreatic cancer.

5 Q. Ko does not expressly teach using
6 liposomal irinotecan as part of the FOLFIRINOX, as a
7 modified FOLFIRINOX regimen, correct?

8 MR. SUH: Objection to form.

9 THE WITNESS: Well, Ko doesn't explicitly
10 teach that. A POSA would understand that the
11 standard combination regimen for advanced
12 pancreatic cancer is FOLFIRINOX and would
13 understand that Ko is saying, okay, we may have
14 a better irinotecan and that this drug may have
15 a potential role in the first-line setting and
16 as part of combination regimens for advanced
17 pancreatic cancer.

18 Are they saying add it to gemcitabine
19 first-line? Are they saying add it to
20 gemcitabine and nab-paclitaxel first-line? Or
21 are they saying substitute it for FOLFIRINOX,
22 irinotecan FOLFIRINOX, or all of the above?
23 It's hard to tell.

24 But the simplest and most plausible and
25 most likely to succeed one of those three is

1 just substituting, popping out the irinotecan
2 and popping in liposomal irinotecan.

3 (Exhibit 1007 was marked for
4 identification.)

5 BY MS. MATTES:

6 Q. You can put that to the side, and you can
7 pull out Saif, which is Exhibit 1007.

8 Do you have it in front of you,
9 Dr. Ratain?

10 A. I do.

11 Q. Okay. Saif reports on results from the
12 NAPOLI-1 study, correct?

13 A. Yes.

14 Q. Okay. And the NAPOLI-1 study was a trial
15 conducted with liposomal irinotecan, 5-fluorouracil,
16 and leucovorin, correct, in combination?

17 A. Yes.

18 Q. And oxaliplatin was not used in this
19 study, right?

20 A. That's right.

21 Q. Okay. And Saif does not disclose the
22 dosing regimen that was used in the NAPOLI-1 study,
23 correct?

24 A. That's right.

25 Q. So a POSA, based on Saif, would not know



1 which dosing regimen achieved the results reported
2 here; is that right?

3 A. I'd have to look at the cited press
4 release.

5 Q. You did not include as one of the exhibits
6 you relied on the cited press release, correct?

7 A. I did not, no.

8 Q. Okay. So based at least on Saif alone, a
9 POSA would not know which dosing regimen achieved
10 the results reported here?

11 A. No, no, that's not why I -- that's not why
12 I cited this article.

13 Q. That's not my question.

14 My question is, based on Saif alone, a
15 POSA would not know which dosing regimen achieved
16 the results reported, correct?

17 A. Not based on this document alone.

18 Q. Okay. You can put this to the side.

19 Can we turn to Paragraph 114 of your
20 declaration. It's on Page 46 of your expert
21 declaration.

22 Are you there?

23 A. I'm there.

24 Q. Okay. And if, actually, you'll turn to
25 the top of Page 47, in this section, you're talking



1 about the Bayever reference; is that right?

2 A. Yes.

3 Q. Okay. And the second full sentence from
4 the top of the page, you write, "Bayever and
5 Fitzgerald are the same inventors of the '552
6 Patent."

7 Do you see that?

8 A. Yes.

9 Q. Why did you make that observation?

10 A. I don't recall.

11 Q. Was it relevant in any way to your
12 opinions?

13 MR. SUH: Objection to form.

14 THE WITNESS: I just don't recall sitting
15 here today reading everything in a vacuum, and
16 without reading the whole scope of my report, I
17 can't tell you.

18 MS. MATTES: Okay. If we can go off the
19 record for a second.

20 MR. SUH: Sure.

21 (Whereupon, a recess was taken
22 from 12:35 p.m. to 12:44 p.m.)

23 BY MS. MATTES:

24 Q. Dr. Ratain, right before the break, I was
25 asking you about one of the sentences on the top of

1 Page 32, I believe.

2 Are you there?

3 A. In my report, you're talking about?

4 Q. Yes, yes, in your expert declaration.

5 A. Okay.

6 Q. That's not it. Sorry.

7 MR. SUH: Counsel, did you say Page 32? I
8 think we left off on --

9 MS. MATTES: I did. But I meant -- it's
10 47. I apologize. I said the wrong number.

11 BY MS. MATTES:

12 Q. And it was the statement where you wrote,
13 "Bayever and Fitzgerald are the same named inventors
14 of the '552 Patent."

15 Do you see that?

16 A. Yes.

17 Q. I asked you if you thought -- if that
18 statement or the -- excuse me.

19 I asked you if the fact that Bayever and
20 Fitzgerald are the same as the named inventors of
21 the '552 patent was relevant to your opinions in any
22 way.

23 Do you recall that?

24 A. I do.

25 Q. And you stated that you didn't recall; is

1 that right?

2 A. I didn't recall sitting here just off the
3 top of my head. I mean, and I would have to read
4 through everything to give you a definitive answer
5 on that.

6 Q. So do you have an opinion as to whether
7 it's not relevant to any of your opinions today?

8 A. I have no opinion about that fact.

9 Q. Okay. In forming your opinions, did you
10 consider whether liposomal irinotecan had nonlinear
11 pharmacokinetics?

12 A. Well, I'm sure it does because irinotecan
13 has some nonlinear pharmacokinetics.

14 Q. And did you consider whether oxaliplatin
15 had nonlinear pharmacokinetics?

16 A. No.

17 Q. Do you know one way or the other whether
18 it does?

19 A. Not off the top of my head.

20 Q. In forming your opinions, did you consider
21 whether leucovorin has nonlinear pharmacokinetics?

22 A. No, because it wouldn't matter. That's
23 plenty of leucovorin no matter what its
24 pharmacokinetics are. It's just a vitamin.

25 Q. And then the same question for

1 5-fluorouracil.

2 Did you consider whether 5-fluorouracil
3 has nonlinear pharmacokinetics?

4 A. Well, it does, but it depends how you give
5 the drug. The bolus is really where you run into
6 problems with nonlinear pharmacokinetics when you
7 give it by infusion. It really doesn't, except
8 perhaps if you had somebody that's genetically B2b
9 deficient, and then you'll run into a problem
10 because they won't be able to metabolize the drug.

11 Q. Okay. Thank you. You can put your report
12 to the side.

13 If you don't mind pulling back out the
14 patent, the '552 patent I should say.

15 Let me know when you have that in front of
16 you.

17 A. I have it.

18 Q. Okay. If you go to Column 30, Line 5.

19 Do you see here where it says "Arm 1 dose
20 modifications"?

21 A. Yes.

22 Q. Okay. And here, it states that the
23 starting dose of Onivyde will be 60 milligrams per
24 meter squared, 5-fluorouracil 2400 milligrams per
25 meter squared, leucovorin 400 milligrams per meter



1 squared, and oxaliplatin either 85 milligrams per
2 meter squared or 60 milligrams per meter squared.

3 Do you see that?

4 A. Yes.

5 Q. And so here, it's reporting on the
6 starting doses for each of these components, right?

7 A. Yes.

8 Q. Okay. And it's your understanding that
9 these are the same starting doses as recited in
10 claim 1 of the '552 patent, correct?

11 MR. SUH: Object to the form.

12 THE WITNESS: Well, claim 1 of the '552 is
13 included within the doses listed in Column 30,
14 Lines 5 through 7.

15 BY MS. MATTES:

16 Q. Right. And so claim 1 recites the same
17 starting doses that is recited in Column 30,
18 correct?

19 MR. SUH: Objection to form.

20 THE WITNESS: I couldn't quite hear that.
21 You had your finger over your mouth.

22 BY MS. MATTES:

23 Q. Sorry. I apologize for that.

24 And so claim 1 of the '552 patent recites
25 the same starting doses that are recited in

1 Column 30 starting on Line 5, correct?

2 A. Well, Column 30, Line 5, says that
3 oxaliplatin will be either 85 or 60, and claim 1
4 says 60.

5 MS. MATTES: I see. Okay. All right. I
6 don't have any further questions. So I
7 appreciate your time, Dr. Ratain.

8 MR. SUH: I don't have any questions.
9 The witness reserves the right to review
10 and sign.

11 MS. MATTES: Of course.

12 (Whereupon, the deposition was
13 concluded at 12:52 p.m. Central
14 Daylight Time.)
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1 CSPC Pharmaceutical v. Ipsen

2 Case No. IPR2025-00505

3
4 I hereby certify that I have read the
5 foregoing transcript of my deposition, given on
6 October 24th, 2025, at the place aforesaid,
7 consisting of pages 1 through 128, inclusive, and I
8 do again subscribe and make oath that the same is a
9 true, correct, and complete transcript of my
10 deposition so given as aforesaid, as it now appears.

11 Please check one:

12 _____ I made no corrections

13 _____ Number of errata sheets submitted

14
15 _____
MARK J. RATAIN, M.D.

16 ALSO PRESENT: _____
17

18 SUBSCRIBED AND SWORN TO
19 before me this ____ day
20 of _____ 2025.

21 _____
Notary Public
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CASE NAME: CSPC Pharmaceutical v. Ipsen
DEPOSITION OF: Mark J. Ratain, M.D.
DATE TAKEN: October 24th, 2025

[illegible]

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C E R T I F I C A T E

The within and foregoing deposition of the witness, MARK J. RATAIN, M.D., conducted via Zoom, was taken before GREG S. WEILAND, CSR, RDR, CRR, commencing at 8:59 o'clock a.m., on the 24th day of October, 2025.

The said witness was first duly sworn and was then examined upon oral interrogatories; the questions and answers were taken down in shorthand by the undersigned, acting as stenographer; and the within and foregoing is a true, accurate and complete record of all the questions asked of and answers made by the aforementioned witness at the time and place hereinabove referred to.

The signature of the witness was not waived and the deposition was submitted to the deponent as per copy of the attached letter.

The undersigned is not interested in the within case, nor of kin or counsel to any of the parties.

Witness my signature on this 26th day of October, 2025.

A handwritten signature in black ink, appearing to read 'G. Weiland', is written over a horizontal line.

GREG S. WEILAND, CSR, RDR, CRR
License No. 084-003472



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