

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC PHARMACEUTICAL GROUP LIMITED,
CSPC OUYI PHARMACEUTICAL CO., LTD.,
CONJUPRO BIOTHERAPEUTICS, INC., and APOTEX INC.,
Petitioners,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

IPR2025-00505
Patent 11,344,552 B2

Record of Oral Hearing
Held: May 19, 2026

Before ZHENYU YANG, TAWEN CHANG, and
TIMOTHY G. MAJORS, Administrative Patent Judges.

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and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P-R-O-C-E-E-D-I-N-G-S

1:00 p.m.

JUDGE YANG: All right. Good afternoon. This is a hearing for IPR2025-00505. I'm Judge Yang. Joining us via video are Judges Chang and Majors. Now counsel, please introduce yourself and let's start with Petitioner.

MR. SUH: Good afternoon, Your Honors. My name is Howard Suh from the law firm of Fox Rothschild representing Petitioner. And with me are my partners Lukas Toft and Joseph Chen. We also have in the audience, our client Dr. Tony Yang from CSPC, as well as our expert witness, Dr. Ratain. And before we start I would like to see if I could hand out hard copies of our demonstratives. May I approach?

JUDGE YANG: Sure.

MR. SUH: I wasn't aware we were going to have remote judges, so I can't give them hard copies. I apologize.

JUDGE YANG: They have digital copies, but thank you.

MR. SUH: And I have one for the court reporter.

JUDGE YANG: Before we start let's have counsel for the Patent Owner introduce themselves first.

MR. GLASS: Good afternoon, Your Honors. Counsel, James Glass for Patent Owner, Ipsen. You won't be hearing much from me today. Presenting on behalf of Ipsen will be my colleague and backup counsel, Mr. Angus Chen, Catherine Mattes, and Elizabeth Murphy. I'll also point out that we have visiting today TJ Paxton, the Director of Intellectual Property at Ipsen. Thank you.

1 JUDGE YANG: Thank you. And welcome everyone. I just have a
2 few things I want to say. Please sit down and I'll let you know when it's
3 time. As we said in the trial order, each party has 60 minutes to present this
4 argument. We'll start with Petitioner and Patent Owner will respond. Both
5 parties may, if you want to, reserve no more than 20 minutes for rebuttal.
6 The court reporter will provide a transcript for this hearing, and it will serve
7 as the official record. To ensure that we have a clear transcript later to help
8 us and you to review it, please clearly identify for the record if you're on
9 Slide 5, say you are on Slide 5, if you are on the patent, say which column,
10 which line, that will be great. As a reminder, demonstratives are not
11 evidence, so please do not present anything new. No new evidence, no new
12 arguments. And if you think the opposing counsel is making a new
13 argument, you may object, but we ask you not to disrupt the other side. Just
14 wait till it's your time and if Patent Owner does it in sur-rebuttal time, we'll
15 give Petitioner time afterwards. That's all I have. Do you have any
16 questions? No?

17 MR. SUH: No, Your Honor.

18 JUDGE YANG: Then, Petitioner, how much time would you like to
19 reserve for rebuttal?

20 MR. SUH: Yeah, we'd like to reserve ten minutes for rebuttal.

21 JUDGE YANG: Okay.

22 MR. SUH: And our opening arguments are going to be split between
23 me and my partner, Mr. Toft.

24 JUDGE YANG: Okay.

25 MR. SUH: So, Your Honor, if we could just begin. These are the
26 Challenged Claims of the '552 patent. The issue here, methods of treating

1 metastatic pancreatic cancer in a human who has not previously been treated
2 with an anti-cancer agent that's been called, in this case, first-line treatment
3 with a specific combination of chemotherapy drugs. That's 60 milligrams
4 per meter square of liposomal irinotecan, 60 milligrams per meter square of
5 oxaliplatin, 400 milligrams meter square of leucovorin, and 2,400
6 milligrams meter square of 5-FU. But Patent Owner, they did not invent this
7 particular combination of drugs to treat first-line metastatic pancreatic
8 cancer because, as is undisputed by this time, the gold standard for treating
9 this class of patients, first-line patients was something called FOLFIRINOX.
10 And FOLFIRINOX stands for folinic acid, which is leucovorin, 5-FU, which
11 is 5-FU, irinotecan and oxaliplatin, right? And this particular gold standard
12 FOLFIRINOX was disclosed in the prior art by Conroy and his protocol
13 appendix and NASA.

14 JUDGE YANG: So, Counsel, before you move on to the next slide, I
15 just want to make sure -- can we go back?

16 MR. SUH: Yes.

17 JUDGE YANG: Slide 12. There is a parenthesis says, first-line
18 treatment, that's Petitioner's addition to the claim. It's --

19 MR. SUH: Right. Exactly. This is a -- this is not a direct quote of
20 the claims, but we have direct quote of the claims later. But this is just to
21 explain that, that phrase, human who has not previously been treated with an
22 anti-cancer agent, that is -- that's been -- that's known in the art as first-line
23 treatment.

24 JUDGE YANG: So the -- that term, a human who has not previously
25 been treated with an anti-cancer agent means first-line treatment?

26 MR. SUH: Yes.

1 JUDGE YANG: And does it matter whether it's a starting dose or
2 later after the starting dose? The second?

3 MR. SUH: Right. So for purposes of this case, what this means first-
4 line treatment, it means that there was no previous regimen of these
5 combination of drugs given to the particular patient. Now, obviously these
6 claims are broad enough to cover first starting doses, but also subsequent
7 doses because as you'll see, I'll explain in a further slide, the actual language
8 of the claims require in Claim 1, that the dose be given once every two
9 weeks, right? And then Claim 5 actually says it has to be given on Day 1
10 and Day 15 of one cycle. Right? So it -- so internally the claims cannot
11 mean that on the second dose you could not have allowed for an anti-cancer
12 treatment to be administered because then the claims would be internally
13 inconsistent.

14 JUDGE YANG: Well, how about -- say the -- this patient has been
15 treated with the -- let me think about that. All right. You may go on. I don't
16 want to hold you off, but I --

17 JUDGE CHANG: Actually, this is Judge Chang. Can I ask a
18 question related to what Judge Yang was asking?

19 MR. SUH: Yes.

20 JUDGE CHANG: So it's your position that if you apply, let's say 85
21 milligram per the -- 85 starting dose of liposomal irinotecan, and then you
22 apply later, you reduce the dose, let's say to 50, and the claim requires, you
23 know, 60. So you're saying that does not -- that still falls within a patient
24 that has not previously received an antineoplastic agent?

25 MR. SUH: That's right. That -- that's correct. But I think --

26 JUDGE CHANG: And what --

1 MR. SUH: But I think for purposes of that specific combination, it's
2 not the liposomal irinotecan that's really at issue with respect to whether it's
3 a starting dose. Because the liposomal irinotecan disclosure that we have
4 here, which is the Bayever reference that's -- that administers it as a starting
5 dose as well.

6 JUDGE CHANG: Right. I think I was using that as example. I think
7 that oxaliplatin is the one that --

8 MR. SUH: That's correct.

9 JUDGE CHANG: -- you're arguing about. What is the -- what is the
10 evidence, intrinsic evidence for saying that that's how the claim should be
11 interpreted?

12 MR. SUH: The intrinsic evidence is the claims themselves, and I can
13 actually put in -- I deal with this here with the actual language of the claims.
14 Right?

15 JUDGE CHANG: Well, how -- sorry, how does the actual language
16 of the claim --

17 MR. SUH: Yeah.

18 JUDGE CHANG: -- show that?

19 MR. SUH: So -- because it says -- the claim actually says a method
20 of treating metastatic adenocarcinoma of the pancreas in a human patient
21 who was not previously received an antineoplastic agent, right? And then
22 this method comprising administering an antineoplastic therapy to the
23 patient once every two weeks. Right? So you provide -- you actually
24 practice this claim on the first day, and then after two weeks, you're
25 supposed to administer this again. So if not previously been received for an
26 anti-cancer drug, means that you could not have put in these actual claim

1 elements, then Claim 1 wouldn't make any sense. And Claim 5 wouldn't
2 make any sense because Claim 5 says the method of Claim 1, wherein
3 liposomal irinotecan, oxaliplatin, and Leucovorin are administered on Days
4 1 and 15 of a 28-day treatment cycle, right?

5 So after two weeks, the dose -- the doses can be reduced and still
6 practice in -- you could still practice this claim. And then after one full
7 treatment, the doses could still be reduced and you could still practice this
8 claim. Right? Because this is not -- this is not a method of treatment where
9 the patient is only given one starting dose. This is not like gene therapy,
10 right? This is -- and this is not how chemotherapy works. The claims may
11 comprise a starting dose, but they also cover subsequent doses. And in
12 Patent Owner's briefing, they conceded that the claims are not limited to
13 starting doses. That they only comprise of starting dose. Right?

14 JUDGE YANG: So we are saying that the 60 milligram per meter
15 square of oxaliplatin --

16 MR. SUH: Yes.

17 JUDGE YANG: -- is the starting dose?

18 MR. SUH: That is the starting dose.

19 JUDGE YANG: Okay.

20 MR. SUH: Correct.

21 JUDGE CHANG: So, to follow-up just quickly, I don't know if it's
22 related, but so I can see an interpretation where you would say, yes, you can
23 receive 60 milligram per meter square if you receive a starting dose, you
24 could receive that once every two weeks. But if you -- if you don't receive
25 that as initial dose, I can see an argument where they said, well, that person
26 has already received a dose that's different than what the claim requires.

1 And so that initial -- so it does seem that there may be a difference between
2 the starting dose and the non-starting dose. So how would you respond to
3 that?

4 MR. SUH: Well, I think that -- in that situation, I think the claims
5 would still be broad enough to cover subsequent doses and even a
6 subsequent dose on a second cycle, Your Honor, right? So what we're
7 saying is that for this oxaliplatin element right there, I don't think there's any
8 dispute on the record that the prior art through Conroy and through its
9 protocol and appendix, it does explicitly teach a lower dose of 60 milligrams
10 per meter square after a starting dose. But even if it didn't, right? Even if
11 Petitioner -- even if Patent Owner tries to convince the board that these
12 claims are only limited to a starting dose, we think that there's enough art
13 and motivation for a POSA to be able to actually administer a 60 milligram
14 per liter dose of oxaliplatin based upon the prior art, based upon what was
15 already known about the toxicity issues regarding FOLFIRINOX. Does that
16 answer your question, Judge Chang?

17 JUDGE CHANG: Yes. Yes. I think we can move on.

18 MR. SUH: Thank you. Just want to go back to where -- okay. So
19 here we are. The Challenged claims versus FOLFIRINOX, right? So the
20 dispute between the prior art and the Challenged Claims has to do with the
21 fact that in FOLFIRINOX, it actually administered something called free
22 irinotecan, a non-liposomal irinotecan, right? And in FOLFIRINOX it was
23 administered at 180 milligrams per meter square. And then the other dispute
24 has to do with this oxaliplatin issue, which we just discussed, right? We
25 believe that the prior art through Conroy and its appendix, and its protocol

1 actually discloses a 60 milligram per meter dose of oxaliplatin, even though
2 the original dose to FOLFIRINOX was 85 milligrams, right?

3 So the Challenged Claims are liposomal irinotecan applied to
4 FOLFIRINOX, right? That's what this invention is. They invented
5 something called liposomal irinotecan and they applied it to the
6 FOLFIRINOX regimen. But by this time, there was a lot that the POSA
7 already knew about liposomal irinotecan, right? Claim 1 of the Challenged
8 Claims versus Bayever, this is the comparison. The only difference -- right -
9 - is 60 milligrams per meters oxaliplatin because Bayever did not teach
10 oxaliplatin, but FOLFIRINOX did, right?

11 So it is Petitioner's position that the Challenged Claims are obvious
12 over the combination of FOLFIRINOX and Bayever, right? Because as we
13 can see with respect to the method of treating a first-line patient for our -- for
14 metastatic pancreatic cancer, FOLFIRINOX and Bayever, each teach this,
15 the 60 milligram dose of liposomal irinotecan. Bayever teaches this, of a 60
16 milligrams of oxaliplatin. FOLFIRINOX teaches this. And then for the
17 Leucovorin and the 5-FU doses. I don't think there's been any dispute on the
18 record that both Bayever and FOLFIRINOX each teach those elements,
19 right?

20 So there was strong motivation to combine FOLFIRINOX with
21 liposomal irinotecan, right? Because even though FOLFIRINOX was the
22 gold standard, it was known to have liabilities based upon its toxicity and
23 liposomal irinotecan, which is Patent wOner's own invention, it was
24 developed specifically for the purpose for being a better irinotecan to
25 provide better efficacy with less toxicity. And then we have the prior art

1 references of Saif and Ko that specifically suggested replacing irinotecan
2 with liposomal irinotecan in FOLFIRINOX.

3 And this is just a slide that shows the that there were known toxicities
4 and liabilities with respect to FOLFIRINOX. I don't have to go into this in
5 too much detail. This is Slide 7. It's based upon our Paper 1 Petition at 16
6 and 41. It relies upon Mahaseth, Exhibit 1005 at 1. Dr. Ratain's declaration
7 Exhibit 1002 at Paragraph 67. And even the patent, right? Exhibit 1001.
8 Even the patent explicitly says that there is this gold standard
9 FOLFIRINOX, however, FOLFIRINOX is known to have significant
10 toxicity and use is limited to patients with better performance. Right? This
11 is the idea of having what they call a better irinotecan -- liposomal irinotecan
12 and applying it to the gold standard of FOLFIRINOX.

13 JUDGE YANG: But the gold standard starts with the 85, the O, let
14 me just say the O drug, right?

15 MR. SUH: Correct.

16 JUDGE YANG: So it's not just applying the liposomal form, there is
17 some other change also.

18 MR. SUH: Yes, there is.

19 JUDGE YANG: I think Patent Owner, if I understand them correctly,
20 they say there is this toxicity issue. But they're saying the -- in the art, they
21 would do a change at a time. They wouldn't make -- okay. Let's say not all
22 four. Let's say they wouldn't make changes to two important ingredients in
23 this regimen at the same time?

24 MR. SUH: Right. So because of what was known about
25 FOLFIRINOX was that there already was toxicity issues regarding giving
26 too much oxaliplatin, 85 milligrams. And that prior art said that if the

1 patient develops certain side effects, you would reduce it. The first dose
2 reduction would be from 85 to 60, right? And that was known not just in the
3 Conroy for FOLFIRINOX prior references, but it was known through other
4 references. And that's what a POSA would understand as well, that you
5 could actually reduce the dose from 85 milligrams to 60 milligrams.

6 And again, Your Honors, I want to make this clear, even if, again, the
7 Patent Owner convinced the board that the only issue in this case is this
8 difference between 85 milligrams of oxaliplatin and 60 milligrams of
9 oxaliplatin, the only difference would be that particular ingredient as a dose.
10 These would just be dosing claims. And I think that we've cited a lot of case
11 law, which says that dosing claims are particularly vulnerable to obviousness
12 because especially in the arts that deal with treating patients, adjusting a
13 dose is routine optimization well within the scope of a person of skill in the
14 art.

15 JUDGE CHANG: So this is Judge Chang, I have two questions for
16 you. The first one is, I understand that there is adjustment, but I also
17 understand that Petitioner's argument is that even if there's motivation even
18 to start, even if we say once limited to a starting dose, you have to start with
19 60, that there's a reason to do this because of the known toxicity. So what is
20 the -- what kind of patient population would you be talking about? How
21 would the skilled artisan know what patients apply a 60 milligram per meter
22 square?

23 MR. SUH: Right. So this patient population, based upon the
24 definition of the claims are first-line patients, right? first-line patients who
25 have advanced metastatic pancreatic cancer. These are very sick patients.
26 So there's -- because it's advanced metastatic pancreatic cancer, there is no

1 option for surgery, right? These are very sick patients already. And
2 therefore, the POSITA would know that there was going to be toxicity issues
3 with respect to this type of regimen, especially knowing what he or she
4 knew with respect to the experience for FOLFIRINOX, where, as we just
5 saw, there's abundant disclosure, which says that FOLFIRINOX should be
6 adjusted down.

7 JUDGE CHANG: Well, this is Judge Chang again. So I understand
8 that argument, but since the prior art -- presumably the prior art talks about
9 this particular category of patients, and they start at 85. So what is the
10 reason -- so I guess I'm saying, if the prior art starts 85, despite knowing this
11 toxicity, why would the ordinary skilled artisan move to an initial dose of 60
12 without having, you know, an initial dose of 85? Wait until there's a side
13 effect -- unacceptable side effects -- before they reduce it?

14 MR. SUH: Yeah. So two reasons Judge Chang. So our first reason
15 is that we don't think that these claims are limited to starting doses for the
16 reasons that we just discussed. Otherwise, the claim wouldn't make any
17 sense. Because it has to be administered once every two weeks, right? It
18 has to be administered on Day 28, after Day 14, after Day 1. And that's just
19 one cycle. So --

20 JUDGE CHANG: Okay. That's the claim's argument.

21 MR. SUH: That's the claim's argument. So the claims aren't limited
22 to a starting dose, but even if they were limited to a starting dose, the POSA
23 would actually have the knowledge to be able to even start at 60 milligrams
24 per meter square based upon what was already known about FOLFIRINOX.
25 And the fact that when combining FOLFIRINOX with a liposomal
26 irinotecan, a better irinotecan, that they were going to be mindful to be able

1 to adjust doses to be able to treat these patients, right? Because the POSA
2 would not just have to be limited to say, okay, I'm going to use these
3 particular combinations -- right -- for Patient 1, and Patient 1 might get
4 really sick, but the POSA could then treat Patient 2 with the knowledge that
5 Patient 1 was kind of sick and therefore be able to adjust the dose.

6 JUDGE CHANG: So based on this argument, what is there -- is there
7 any limitation in terms of dosage that you would say it would be not
8 obvious? Because this seems like this could somewhat be applied.
9 Essentially, you're saying that the patient -- there will be routine
10 optimization. So essentially any dose could be routinely optimized. So is
11 there any limitation that you see in terms of what the dosage can be?

12 MR. SUH: Well, I don't think we're arguing that it could be any
13 limitation, Your Honor, because as I mentioned, the prior art actually
14 discloses every single one of those limitations and even those doses. But
15 again, if -- Patent Owner's best case scenario is that the prior art would just
16 motivate the POSA to actually have this claim except for 85 milligrams of
17 oxaliplatin instead of 60 milligrams of oxaliplatin, right? That's their best
18 case scenario, right? But even if that's the case, which we don't think that's
19 the case, right? Because we think the prior art teaches it already, right? This
20 would still just be a dosing claim. And I think that it -- the POSA would be
21 able to routinely optimized down from 85 to 60 because there was evidence
22 of that already in FOLFIRINOX. Does that answer your question, Judge
23 Chang?

24 JUDGE CHANG: Yes. I think we can move on.

25 MR. SUH: Okay. So I do want to reserve some time for my partner,
26 Mr. Toft, would be talking about unexpected results, but I just want to go a

1 little quickly through the prior art. So this is the Ko reference Exhibit 1008,
2 this provides the motivation to actually combine liposomal irinotecan with
3 FOLFIRINOX, right? And within the same publication, this is actually
4 talking about the improvements of liposomal irinotecan over free irinotecan.
5 And these are Phase II studies, Your Honor. Phase II clinical trials, which
6 showed the benefits of liposomal irinotecan in patients -- in pancreatic
7 cancer patients. Saif, a Phase III in clinical trial -- right -- actual results
8 showing the benefits of liposomal irinotecan over irinotecan. And again,
9 there's a clear suggestion that you should be replacing free irinotecan with
10 liposomal irinotecan, right?

11 Dr. Ratain also made these -- provided his expert opinion that you
12 would be able to combine these two pieces of bodies of prior art because
13 there was strong motivation, especially because of Saif and Ko, in addition
14 to Bayever, which also makes that suggestion. There was a reasonable
15 expectation of success because these prior art references actually showed
16 real benefits. FOLFIRINOX was a gold standard, right? Ko and Saif
17 actually showed Phase II and Phase III clinical trial results showing
18 improvement in cancer patients, pancreatic cancer patients, right?

19 And here we -- I think this is where we spent most of this morning --
20 this afternoon's argument the protocol on the supplemental appendix do
21 disclose a dose reduction to 60 milligrams of oxaliplatin. Dr. Ratain -- he
22 concluded that a significant portion of patients undergoing FOLFIRINOX
23 were administered with 60 milligrams per meter dose.

24 And finally, before I turn this over, I just want to talk a little bit about
25 Patent Owner's expert. Okay? So this is ASCO from 2025, right? So here,
26 Dr. Oberstein was on the panel with two other oncologists, and he said that

1 the regimen of FOLFIRINOX and the regimen of NALIRIFOX which is the
2 regimen of the commercial embodiment for the claims, right? These
3 regimes were quite similar, you know? And then he says, again, but, you
4 know, the schedule otherwise for patients was quite similar. But then the
5 panel goes on and they say, look, the original FOLFIRINOX, I don't think
6 any of us use it. It was challenging, right? You now use the modified
7 version, nobody can tolerate the full dose of FOLFIRINOX. NALIRIFOX
8 and FOLFIRINOX were quite similar. That's what Dr. Oberstein opined
9 upon. And that the panel all said that those modifications have to be done
10 for FOLFIRINOX, right? This is what Dr. Oberstein, he was saying that
11 from Day 1. You don't be too aggressive on Day 1, right? It's -- the
12 important thing is to keeping patients on treatment. You don't want to be too
13 strong, too aggressive on Day 1. And I really would ask the board to just
14 play the video, which we have entered into the record, Exhibit 1211. It's
15 only five minutes long. We want to play it today, but I don't think we have
16 time.

17 But again, we don't think that Dr. Oberstein is credible because when
18 he's testifying on behalf of Patent Owner, he says that the FOLFIRINOX
19 and the Challenged Claims are different. Although he says they're quite
20 similar in public. He says that when he's an expert here in the case, he says
21 that you would always administer a maximum tolerated dose, right? But
22 then at ASCO, he says, no, right? You -- the way we practice is that we
23 have to modify doses, right? So -- and of course he's been working with
24 Ipsen Patent Owner for a number of years. So that's all I have. I'd like to
25 turn it over to my partner, Mr. Toft, to talk about unexpected results.

1 MR. TOFT: Okay. If I may, Your Honor, Judge Chang, I'd like to
2 just address your last question. I think my colleague Mr. Suh was
3 explaining. But if we look back, this is Slide 37 and it shows the different
4 trials of different drugs that occurred related to pancreatic cancer. And the
5 second column here is the Ko trial, which alleged the alteration of Conroy.
6 And that trial, if you see was from December, 2005 to October, 2009 and
7 published in 2011. And the record that we have presented, Conroy taught
8 the 85 milligrams per meter square of oxaliplatin. But the protocol, which
9 was published before the study occurred, had already suggested that a
10 toxicity concern should be addressed by lowering oxaliplatin to 65 -- or
11 sorry to 60 milligrams per meter square.

12 And then as seen in the appendix and multiple other references, which
13 some of which, you know, are going to be presented in my discussion,
14 persons of ordinary skill in the art did reduce oxaliplatin due to toxicity
15 concerns and did so in multiple different studies. And the median dose
16 reported in the Conroy supplemental was 78 percent. So that -- a person
17 with ordinary skill looking at this was motivated at the time to address
18 toxicity concerns by dropping it to 60, which as our briefing shows was
19 presented in the Conroy protocol and the appendix.

20 But if I may go back first to the claim requirements, and now this is
21 Slide 33. The claims require three specific limitations, and they require
22 providing a precise dose of four drugs to a human patient on a fixed
23 schedule once every two weeks and to treat metastatic adenocarcinoma.
24 And so to practice these claims, the patient has to receive these specific
25 doses at least twice, two weeks apart. And relevant here, but on our

1 expected results argument, which I'll be talking about, that benefit must be
2 tied to those claimed parameters.

3 Now, Patent Owner's claim that led to the '552 patent were rejected
4 no less than five times, and often based in part on teachings in Conroy or
5 Bayever. Patent Owner then raised an unexpected results argument relying
6 on Wainberg, which are Exhibits 1018 and 19 of the record. And that -- that
7 the claims allowed. But the evidence here does not support an unexpected
8 results finding. Now, to have an unexpected results, you have to have a
9 legal nexus. And sorry, the burden is on the Patent Owner to show the
10 secondary consideration's evidence, and to provide evidence that shows the
11 secondary indicia and to provide a nexus of that benefit or that secondary
12 indicia to the claimed invention. And Patent Owner hasn't done that.

13 Sorry, let me -- and to do an -- hasn't -- sorry, it hasn't provided a
14 nexus. They haven't provided an identification of what was expected, and
15 they haven't shown that it's a difference in kind, and the unexpected results.
16 We often talk about difference in kind versus difference in degree, and the
17 difference in degree is they're fundamentally similar, but the outcomes are
18 usually matter of more or less. Difference in kind, they're usually entirely
19 different properties, totally new functions or behave dissimilar to what was
20 expected. And that is not what we have here. For some reason, my slide is
21 not advancing. Oh, thank you.

22 Now here, Patent Owner makes no serious argument limited to nexus.
23 This paragraph, which is from Page 20 of their surreply, is the only time that
24 they refer to the word nexus in any of their briefing. And here the sole
25 argument put forward is that NALIRIFOX regimen comprises the '552
26 patent's components and doses. And they're going to identify what claim

1 and they provide a citation to Paper 21, the Patent Owner's response and
2 Exhibit 2076, Dr. Oberstein's declaration.

3 Now, if you look at Paper 21, they also include the same cite to
4 Oberstein and reference to Dr. Ratain's depo testimony. But if you look -- I
5 encourage you to look at those citations. The -- Dr. Ratain's testimony does
6 refer to what was claimed by the '552 patent, but makes no mentions to
7 NALIRIFOX. And Dr. Oberstein discusses NALIRIFOX, but makes no
8 mention of what the claims dosage of NALIRIFOX is, or which claim or
9 claims it embodies. That is not in the record.

10 Now, here is the chart that I was showing you earlier. That first
11 column is the NAPOLI-3 study, which primarily relies on for their
12 unexpected results argument. And if we look at that, the -- I'll blow up a
13 piece of that in the column here. The details say the liposomal irinotecan is
14 dosed at 50 milligrams per meter square. And I'll also note that Exhibits
15 1018 and 19, which are the Wainberg references, refer to the same dosing.
16 And that Ipsen's poster, which was published after the institution of this
17 proceeding, or at least after the petition, also states that NALIRIFOX, this is
18 kind of a summation of the NAPOLI-3 study was dosed at 50 milligrams per
19 meter square in this green box, which I'll blow up as well.

20 Now, the claim doses require 60 milligrams per meter square of
21 liposomal irinotecan, and Patent Owner hasn't made any effort to explain
22 how NALIRIFOX relates to the claim's doses, given this information that's
23 in the record. And the NAPOLI-3 dose reductions, even if the dose -- the
24 claimed dose of NALIRIFOX is the same as the claim, the NAPOLI-3 dose
25 reduction breaks that nexus.

1 And I've blown up a few other examples of -- from the Ipsen's poster
2 that you can see here. And as we can see, over half of the participants in this
3 -- I'll run the Table 3 on the right here -- received dose reductions in
4 liposomal irinotecan. Over half of the participants, 60 percent received dose
5 reductions in oxaliplatin, 70 percent received dose delays of liposomal
6 irinotecan, and just under 70 percent received dose delays for oxaliplatin.
7 And the long-term survivors had even more delays in reductions in doses.
8 The long-term survivors there experienced the best outcomes. So their
9 longer life. That skews the overall results of the survivability and
10 tolerability of these patients in the study.

11 And if you look at the long-term survivors, they had 66.7 percent
12 received dose reductions of liposomal irinotecan, and almost 87 percent
13 received dose delays of the same. Eighty percent received dose reductions
14 of oxaliplatin, and 80 percent received dose delays of the same. Now, any
15 one of those, the delays in dosing the reductions, of one or more drugs is
16 enough to destroy the nexus with the claimed invention, which requires
17 specific dosing every two weeks.

18 And Patent Owner's expert Dr. Oberstein, confirms this lack of nexus.
19 He confirmed first that he offers no opinion relating to a finding that there is
20 a nexus, but his testimony confirms that no nexus exists. While we know
21 most patients in the NAPOLI-3 study received both dose reductions and
22 delays, there's no evidence provided that relates to how many patients or
23 which patients received the same dose as the initial dose during their second
24 treatment, their third treatment, or which ones received the claim to dose two
25 weeks apart. And Oberstein confirms he has no knowledge of how many or
26 which patients received a dose reduction after their first treatment. And we

1 know that the patients who did the best are the patients who received the
2 most dose reductions and the most dose delays.

3 So the suggestion is that those who performed the worst got even
4 higher for more consistent doses. And that just shows that any benefit that --
5 that can be attributed to the NAPOLI-3 results cannot be attributed to the
6 claimed invention. Now, in addition to no evidence of nexus to the claim
7 doses or the claim dose schedule, Oberstein confirms that a benefit for
8 anyone treating -- for -- sorry for any one patient, that treatment cannot be
9 known for sure. As he testified, when you're treating, the goal of the
10 treatment is to provide benefit to the patient. But when it comes to any one
11 individual patient, we don't know for sure if they've been treated.

12 Now putting aside nexus. Even if nexus could be shown, Patent
13 Owner hasn't shown what was expected and how the differences between
14 what should have been expected and what was were a difference in kind.
15 Now, the results were not unexpected. Patent Owner -- at best, Patent
16 Owner's Response at Page 52, states that a POSA would understand dose
17 reductions of multiple components in the combination therapy may
18 compromise efficacy. But when they argue this, they cite to Dr. Oberstein's
19 declaration, Exhibit 2076 at Paragraphs 263, 306 to 8 and 288 to 91, and I
20 encourage you to go look at those as well. There is no evidence in Patent
21 Owner's Response that corroborates this understanding other than these
22 citations. And the cited Oberstein testimony, likewise offers no evidence
23 that at the time of the invention in 2015, a person of ordinary skill would've
24 understood that lowering doses in FOLFIRINOX compromised efficacy.

25 Now, the testimony and unexpected results, contrary to Patent
26 Owners' arguments, is not un rebutted. Dr. Ratain offered testimony that

1 POSA's awareness that modifying FOLFIRINOX regimens would result in
2 comparable efficacy. And provided multiple examples in his declaration.
3 I've highlighted just a few of those here on Slide 43. The Patent Owner's
4 expert, Dr. Oberstein, confirms this understanding. The Appendix B,
5 compiled that Dr. Oberstein includes multiple pre-institution and post-
6 institution studies that show dose reductions in FOLFIRINOX. And that
7 they improved both tolerability and did not reduce or increased efficacy.

8 Now, here are some of the examples pulled from Appendix B.
9 Gunturu, in 2012, found dose reductions of oxaliplatin, irinotecan, and 5-FU
10 "Improved tolerability" compared with a full dose FOLFIRINOX and, "Do
11 not reduce the efficacy of FOLFIRINOX in metastatic pancreatic cancer
12 patients." It was in 2012. Also in 2012, Peddi reduced oxaliplatin, irinotecan
13 and 5-FU in first cycle treatments and further reduced all three in subsequent
14 treatments. And Peddi found that, "In spite of dose reductions,
15 FOLFIRINOX was found to be very effective" and had a response rate
16 similar to the ACCORD or Conroy study.

17 Lowrey in 2012 also reduced starting doses of all of the drugs to 80
18 percent of what was disclosed in Conroy and found acceptable toxicity and
19 an overall survival that beat Conroy. Ghorani in 2015 reduced irinotecan
20 and removed the 5-FU bolus and found improved toxicities and,
21 "Comparable efficacy outcomes." Now, there's multiple examples in
22 Appendix B pre and post invention, but this is not unexpected. Reducing the
23 doses was going to address toxicity concerns, and there were multiple
24 examples of a person of ordinary skill in the art doing this.

25 In fact, a 2015 -- June, 2015 publication demonstrates that one of the
26 preeminent medical institutions, the Memorial Sloan Kettering Cancer

1 Center, or MSK as it's sometimes referred to, had identified over a hundred
2 patients that were treated between 2010 and 2013, all of whom were given a
3 starting dose of 80 percent of that in Conroy. Now, 45 percent of those had
4 additional doses thereafter, but as to be expected, there were less toxicity
5 concerns and the median overall survivability was 11 months, or the same as
6 Conroy.

7 Reliance on liposomal irinotecan does not change what was expected.
8 The use of liposomal irinotecan instead of free irinotecan was both
9 suggested by the prior art, but from at least 2007. And this again is with
10 reference to Slide 46. There's three exhibits here that I have cited, but there's
11 more in the record. Exhibits 1008, 1058, and 1059. The prior art suggested
12 that liposomal irinotecan over free irinotecan exhibited, "Greatly enhanced
13 anti-tumor efficacy" and "demonstrated increased efficacy and tolerable
14 toxicity when compared with free irinotecan in pancreatic cancer models."
15 And it had "Superior activity over irinotecan" or free irinotecan.

16 And that just means that, that any difference, if at all, is a difference in
17 degree, not kind. This is a little bit more or a little bit less efficacy, a little
18 bit more, a little bit less tolerability. It is not changing the way the drug
19 works. And Patent Owner relies exclusively on Oberstein's testimony again,
20 to say that this is a difference in kind. But as Oberstein's testimony at
21 deposition highlights that a difference in kind to him means it's nothing more
22 than the same outcome or slightly better and not a step forward, not an
23 innovation.

24 The Patent Owner relied on Wainberg in its prosecution of the '552
25 patents and pre-institution to argue unexpected results. And again,
26 Wainberg's Exhibits 1018 and 1019 of the record. And pre-institution, they

1 argued that Wainberg taught unexpected results because of an increased life
2 expectancy or overall survivability. Now in its Patent Owner's Response
3 and its Sur-reply, Patent Owner doesn't cite to or mention Wainberg at all.
4 But in its discretionary denial briefing, they don't dispute, and even admit,
5 that Wainberg cautions their inherent limitations to its study design. And
6 that included a smaller population size, that included differences in disease
7 stage, differences in disease type, differences in patient ages which Dr.
8 Oberstein references in the video that my colleague Dr. Suh encouraged you
9 to watch.

10 And because of that, there's no dispute and it's repeated throughout
11 that FOLFIRINOX and NALIRIFOX cannot be reliably compared.
12 Comparisons between the two cannot be made to justify an unexpected
13 results claim here. But there's also no dispute that Patent Owner has raised
14 that additional, more recent studies, lack of the inherent limitations that
15 Wainberg identifies and demonstrate a lack of advantage for NALIRIFOX.

16 Turning to Slide 49, when looking at patient outcomes, the industry
17 literature finds, "no difference," between the two regimens, even when
18 FOLFIRINOX had an overall survivability that was higher than the
19 NALIRIFOX. 11.7 months to 11.1 months. And this isn't unlike the
20 difference that Patent Owner argued in prosecution of what reportedly gave
21 rise to the increased overall survivability cited from Wainberg. And there's
22 nothing the Patent Owner has provided that shows that this survival
23 difference is a difference in kind and not just one of degree.

24 The National Comprehensive Cancer Network – turning to Slide 50 --
25 is sometimes referred to as the NCCN. It's a recognized standard in cancer
26 treatment for pancreatic cancer and others, and it has been for decades. The

1 NCCN frequently updates its guidance with the best available evidence and
2 is meant for a tool for practitioners to treat various diseases and suggest
3 which treatments will provide the best outcome. And despite multiple
4 efforts by Patent Owner to change the guidance that NCC suggests, NCC has
5 held steadfast in its conclusion, that NALIRIFOX does not offer an
6 advantage over FOLFIRINOX.

7 And since the Institution Decision, like I said after -- at least after the
8 Petition was filed, but possibly after the institution, I apologize for not
9 knowing the exact date, but Ipsen published this poster, Exhibit 1202, and in
10 the poster on the left hand side under the background, at 16.1 months, Ipsen
11 admits that the NALIRIFOX treatment had a median overall survivability of
12 11.1 months. That's why they walked back this idea of overall survivability
13 and instead of an increased overall survivability, they're saying comparable
14 survivability. Because even their own poster and studies suggest there isn't
15 an increase over FOLFIRINOX. But reducing the doses was expected to
16 reduce the toxicity.

17 And Patent Owner's expert confirms the NAPOLI-3 trial had 11.1-
18 month median survival, the exact same number as the Conroy reported from
19 their trial.

20 Turning to incremental cost effectiveness ratio. Not only is there no
21 clinical advantage, there's also no cost advantage. The incremental cost
22 effectiveness ratio or ICER as it's sometimes called, is a measurement of
23 value for the cost of a drug. And as explained in our briefing, we think the
24 Patent Owner improperly incorporated by reference arguments related to
25 ICER. But even to the extent the Board is willing to consider this evidence -
26 - I have cited or quoted something from Exhibit 1217, Patent Owner put in

1 Exhibit 2029. Both of them show that NALIRIFOX far exceeds the
2 currently acceptable thresholds for economic value and has a zero percent
3 probability of being cost effective.

4 And as I said, this was an improper incorporation by reference. Dr.
5 Oberstein included references to this ICER evidence in his -- sorry
6 declaration, but at his deposition when asked, he stated that he wasn't
7 qualified and couldn't comment on them. And that's Page 390 of Exhibit
8 1210. And in its Sur-reply, Patent Owner doesn't dispute that this ICER
9 values for NALIRIFOX show that NALIRIFOX is just not worth the cost.

10 And then finally, reliance on *Allergan* is misplaced. Patent Owners
11 only claim of a difference in kind versus a difference in degree rests on this
12 case. And if you read this case it's very distinguishable. There are no
13 arguments or evidence here that the prior art taught away from the
14 combination or the claimed invention, as was the case in *Allergan*. And
15 there's no arguments or evidence that safety concerns or side effects from
16 FOLFIRINOX caused patients or practitioners to discontinue the treatment
17 of FOLFIRINOX.

18 The NCCN guideline that I just put up still says FOLFIRINOX is the
19 number one recommended treatment. Dr. Oberstein continues to prescribe
20 FOLFIRINOX today and that can be found at his deposition transcript,
21 Exhibit 1210, Page 78, Lines 14 to Page 79, Lines 3. This is just in opposite
22 case to the facts that issue here. And our position is that these results are not
23 unexpected and this is a difference in degree at most.

24 MR. CHEN: Judge may I approach?

25 JUDGE YANG: Yes. How much time would you like to reserve?

1 MR. CHEN: I think we could reserve 15 minutes for rebuttal, please.
2 Yes. Good afternoon. May it please the Court. Angus Chen of Quinn
3 Emanuel on behalf of Patent Owner, Ipsen. The invention here is a
4 significant advancement in the treatment of a very serious disease state. It's
5 combining a new drug, liposomal irinotecan and it combines it with three
6 other chemotherapy drugs, so a total of four in the regimen, at very specific
7 doses to delicately balance not only safety, but efficacy. We've heard a lot
8 today about toxicity. I can't imagine that Petitioner would urge that we can
9 ignore efficacy when treating metastatic pancreatic cancer patients who have
10 less than a year to live in general. I'm sure that they wouldn't ignore efficacy
11 considerations, but the fact that we heard so much about toxicity and nothing
12 about efficacy really just is illustrative of how their argument is based on
13 hindsight and selectively pulling out information from the prior art to piece
14 together their obviousness argument.

15 JUDGE YANG: I thought the Petitioner actually did point to some
16 kind of evidence where the efficacy was maintained, or --

17 MR. CHEN: I didn't hear it, but I'll be sure to address the references
18 that they rely on. I just meant for today's oral argument, there was a lot of
19 focus on toxicity and not much on efficacy today, I'm sorry if I was
20 confusing that. And so the invention at hand ultimately became a dosing
21 regimen that's been called NALIRIFOX. That regimen is very specific to
22 the doses that we see in the drugs that we see. For convenience, I'll skip the
23 milligrams for meter square just to make the conversation easier, but it's 60
24 of liposomal irinotecan, which is different than irinotecan, 60 of oxaliplatin,
25 200 of -- or 400 depending on the type of leucovorin, and 2,400 of 5-FU
26 without the bolus. Now, as we all know, this is a method of treatment claim

1 and I just want to take a moment to remind ourselves of where we are in the
2 record.

3 So Petitioner filed a Petition, put in an expert declaration in support of
4 it by Dr. Ratain. He advanced two claim constructions, primarily relying on
5 one, the alternative being to relate it to a priority date, which they're not
6 advancing here. Now, the primary claim construction did not require any
7 actual efficacy. The Board rejected that construction and it came up with its
8 own construction that said that treatment requires something more than a de
9 minimis effect. After that Patent Owner put in this reply with a supporting
10 declaration from Dr. Oberstein and Petitioner put in its Reply, but without
11 any expert declaration from Dr. Ratain or any expert.

12 What we have on this record then is a failure of proof. They have --
13 Petitioner has no expert applying the Board's claim construction of treating
14 to its argument. Now, I'll speak to -- sorry, I forgot to articulate our division
15 of argument. I want to --

16 JUDGE YANG: So on that issue, are the two experts' understanding
17 of treatment different?

18 MR. CHEN: That's why I'm urging, Your Honor, because Dr.
19 Ratain's opinions were based on his claim construction that was rejected by
20 the Board. He never put in a subsequent claim, a declaration applying the
21 Board's claim construction. Patent Owner's expert, Dr. Oberstein, did adopt
22 the Board's claim construction in forming his opinions. So --

23 JUDGE CHANG: This is --

24 MR. CHEN: Yes, Your Honor.

25 JUDGE CHANG: I'm sorry, this is Judge Chang. So is it Patent
26 Owner's position that -- because I think the Petitioner's expert did provide

1 evidence, and Petitioner did provide evidence of the de minimis therapeutic
2 effect. So is it Patent Owner's position that there must be an expert opinion
3 applying the claim construction before we can find for the Petitioner?

4 MR. CHEN: That is our position, Your Honor. Especially with
5 respect to reasonable expectation of success. It's our position that there are
6 no expert opinions applying the Board's claim construction requiring more
7 than a de minimis effect in particular reasonable expectation of success.

8 JUDGE YANG: So, looking at Exhibit 2076, which is your expert's
9 declaration, Paragraph 139, he says, "While some patients may not receive a
10 therapeutic benefit, the intention behind any treatment is for such benefit to
11 occur." So, comparing that with Dr. Ratain's declaration defining treat,
12 which is attempt or with intent to cause therapeutic improvement in the
13 patient. Could you elaborate a little bit on this? In comparing these two
14 statements, what's the critical difference?

15 MR. CHEN: Well, Dr. Ratain's opinions that he applied with his
16 claim construction expressly say no actual efficacy, whereas Dr. Oberstein's
17 opinions apply with the board's claim construction. So let me just fast
18 forward to -- I meant to say that I will be addressing the prima facie case of
19 non-obviousness. And my colleague, Ms. Mattes, will be addressing
20 unexpected results and Grounds 2, possibly 3. Okay. Sorry, I'm on Slide 7
21 now. This is just a summary of Dr. Oberstein's credentials. He's a highly
22 credentialed pancreatic cancer physician, Co-Director at NYU Pancreatic
23 Cancer Center, has personal experience with the main regimens that we're
24 talking about here and the main drugs that we're talking about here. He's
25 consulting practice with pharmaceutical companies, he's standard in the
26 industry.

1 While not mentioned here, I guess in the papers, there was much
2 about the compensation that he received. I just know for the record it was
3 less than five percent of his income. And again, while there's a lot of
4 attorney argument accusing him of bias, there was no reply expert
5 declaration to provide foundational opinions to support any alleged bias.

6 So turning to Slide 11, we have the claims here, and earlier there was
7 a discussion about the starting or initial dose. I believe I heard Petitioner
8 admit this morning that the 60 milligrams per meter square of oxaliplatin is
9 in fact the starting dose. Judge, you asked what's the intrinsic evidence for
10 their position? I would submit there is none. The intrinsic evidence for
11 Patent Owner's position are on the slide here at the '552 Patent, Column 13
12 and Column 30, where it expressly describes the doses recited in the claim
13 as starting or starting patient's initial doses.

14 And to your point, that only makes sense because these are patients
15 who have not previously received any cancer agent. And Petitioner
16 misunderstands the issue here. We are not saying that the claims are limited
17 to the starting dose, we're saying that they require that they begin it with that
18 starting dose. And then as these excerpts on Slide 11 show, you may adjust,
19 but the starting dose is required. There's also been a lot of discussion about
20 dose reduction, and I just want to clarify something. It can be very
21 confusing sometimes because there's a dose reduction after you start with a
22 higher dose if for some reason the physician wants to do that. There's also a
23 dose reduction that gets confusing with Petitioner's arguments because
24 they're comparing it to prior art standards.

25 So that's part of the problem here in their argument, which is they're
26 conflating different concepts. And we can't look at numbers divorced from

1 their concepts like in Conroy, where the starting dose is 85 milligrams per
2 meter square.

3 And so on Slide 12, we look at, this is an illustration of the
4 comparison of the two regimens: the primary regimen that Petitioner relies
5 on FOLFIRINOX and the claim regimen also called NALIRIFOX. There
6 are four changes that are required to get from FOLFIRINOX to
7 NALIRIFOX under Petitioner's theory. One, you have to replace irinotecan
8 with a completely different drug. That's undisputed. I will show you later
9 Dr. Ratain agrees that it's a different drug with different properties. Number
10 2, the dose of irinotecan needs to be lowered from 180 to 60. Number 3, the
11 starting dose of oxaliplatin has to be reduced from 85 to 60. And Number 4,
12 the starting dose of 5-FU has to be lowered in the sense that the bolus dose is
13 not given.

14 JUDGE YANG: Would you entertain the idea of Bayever actually
15 teaches three out of the four recited drugs and the only one missing is
16 oxaliplatin?

17 MR. CHEN: I agree that oxaliplatin is missing from Bayever. I think
18 that's a significant issue because both irinotecan and oxaliplatin have similar
19 toxicities in neutropenia, which is a low white blood cell count. And so
20 there is no motivation articulated why we would combine oxaliplatin with
21 liposomal irinotecan when they both have similar toxicity issues, especially
22 when the liposomal irinotecan has a -- an extended release of the irinotecan
23 and thus potentially exposing the patient to even more toxicity. So that's
24 first. Secondly, Bayever does not teach the 60 milligram per meter squared.
25 So that's one of the four issues that I just raised. Its starting doses are 120
26 milligrams per meter squared or 80 milligrams per meter squared for

1 liposomal irinotecan. So I would respectfully submit that at least those two
2 differences can be found with Bayever.

3 JUDGE CHANG: This is Judge Chang.

4 MR. CHEN: Yes.

5 JUDGE CHANG: Sorry. In terms of the motivation since Conroy for
6 FOLFIRINOX already suggests combining oxaliplatin and irinotecan, why
7 wouldn't it be obvious to add that to -- so you mentioned toxicity, but that
8 seems to be something that's already present in some of the known prior
9 combinations?

10 MR. CHEN: Right, so Conroy for FOLFIRINOX had a different
11 dose of oxaliplatin, 85 milligrams per meter squared, and the conclusion of
12 Conroy is based on that dose. So when the patients are lowered because of
13 their toxicity, that's not what the conclusion is for -- is based on for Conroy.
14 Slide 17 shows you an excerpt of Conroy and they're defining the regimen as
15 85 milligrams per meter squared. How do we know that and how do we
16 know that's the overall teaching of the art? Because in Slide 18, two years
17 later, the same Conroy author is telling everybody in 2013, FOLFIRINOX is
18 85 milligrams oxaliplatin. And two years after that in 2015, others in the art
19 are also calling FOLFIRINOX 85 milligrams oxaliplatin.

20 The conclusions of Conroy as illustrated in Slide 19 are not based on -
21 - efficacy conclusions are not based on anything above 85 milligrams per
22 meter squared oxaliplatin. The basis for that in Conroy was a reference
23 called -- I apologize if I'm mispronouncing it, Ychou Exhibit 2038, which is
24 cited in Conroy. That reference recommended a starting dose of 85
25 milligrams per meter squared oxaliplatin in order to be efficacious. And in
26 Slide 20 --

1 JUDGE MAJORS: Mr. Chen?

2 MR. CHEN: Yes.

3 JUDGE MAJORS: Mr. Chen, this is Judge Majors. Can I interrupt
4 you for a moment?

5 MR. CHEN: Yes.

6 JUDGE MAJORS: So I just want to make sure I understand Patent
7 Owner's perspective on the scope of the claim. And I'm going to give you a
8 hypothetical. So let's imagine that we have a patient and they start, their
9 very first dose is 60 milligrams per meter squared of the liposomal
10 irinotecan, 85 milligrams per meter squared of the oxaliplatin, 200 of
11 Leucovorin, and 2,400 of the 5-FU. And then in a second and third
12 administration of the next two weeks and month, the oxaliplatin is then
13 reduced to 60 milligrams. Is that covered by Claim 1?

14 MR. CHEN: I'm sorry, I thought I followed you, but in the beginning
15 of your hypothetical, the starting dose is how much oxaliplatin?

16 JUDGE MAJORS: Maybe I misspoke, I meant to say 85. So it's
17 above -- the very first dose of oxaliplatin is 85 and then it is reduced for
18 administration two, three, etc., to 60. Is that inside or outside the scope of
19 Claim 1?

20 MR. CHEN: Outside, sir. Because the starting dose, as we discussed
21 earlier, must be 60 milligrams per meter squared. And that's the issue with
22 Conroy that we're selectively ignoring when we listen to Petitioner. Conroy
23 teaches you at most start 85 and then do things such, including one of them
24 is turn it down to 60. So there is no conclusion in Conroy about 60
25 milligrams per meter squared. It started at 85 and then make an adjustment.

1 And let me just show you what those adjustments are that Petitioner is
2 ignoring. I'm on Slide 21 now, and this is the Conroy Protocol.

3 So in Conroy, the patient starts with 85 milligrams per meter squared
4 oxaliplatin, we'll just focus on that one drug out of the four. Okay? Then it
5 says as exemplified here in Slide 21, if there is a neutropenia reaction, that's
6 PNN there on the left row, you go over to the dose reduction and it says
7 reduce the dose for every single drug, not just oxaliplatin. And in fact, the
8 first episode it says reduce irinotecan to 150 and it says for oxaliplatin, don't
9 reduce the dose. That's the first event. And then it makes a recommendation
10 for the other drugs. Then the second event, you maintain irinotecan at 150
11 and then you reduce oxaliplatin to 60. That's the context for Conroy.

12 It's not 60 oxaliplatin with blinders on, it's 85. And then you do see a
13 first episode, do nothing with oxaliplatin, see a second episode, and that
14 patient who got 85 initially can then get dialed down to 60. That's what
15 Conroy's teaching us. So Petitioner's argument is just cherry picking from
16 these disclosures to piece together and try to tie it to the claims.

17 JUDGE YANG: I have a perhaps related question, but not exactly on
18 Conroy. About claim language. The first question during this hearing
19 actually was about Petitioner's parenthesis saying it's a first-line treatment.
20 And that language is in Claim 1, it says, A human patient who has not
21 previously received an anti-neoplastic agent. Petitioner represents that's a
22 term of art and it means first-line treatment. Do you agree with that?

23 MR. CHEN: I agree with that.

24 JUDGE YANG: Okay. So if you agree with that, –what is your
25 support for saying this is actually the starting dose. What's the support
26 saying this has to? I mean, I understand you are arguing it's not limited to

1 starting dose, it includes the subsequent cycles, but what's the support for
2 arguing it has to include the starting dose?

3 MR. CHEN: Because the Specification as clipped in Slide 11 says
4 that these are the initial doses. So that's the regimen. Dr. Oberstein also
5 opined as such in his declaration at Exhibit 2076, Paragraph 119, and there
6 was no rebuttal opinion from Dr. Ratain or any other expert on this issue.

7 JUDGE YANG: All right. So, on the issue of 60 milligram per
8 square meter oxaliplatin, there may be more, but right now I am looking at
9 one piece of prior art Petitioner actually relies on, that's that Cantore
10 reference.

11 MR. CHEN: Yes.

12 MR. CHEN: Exhibit 1009. There, I think the starting dose is 60. I
13 understand it doesn't include certain other drugs, but would you address
14 that?

15 MR. CHEN: Yes, Your Honor. I'm on Slide 16 of our slides. This
16 reference is further illustrative of Petitioner's hindsight. When asked how
17 Dr. Ratain found this reference, he said, oh, because counsel asked me go
18 find something with 60 milligrams oxaliplatin. That's hindsight. He wasn't
19 assessing the prior as a whole. More importantly, however, to your
20 question, Cantore starts with 60, but the conclusion is, "Future studies
21 should try higher doses of irinotecan and oxaliplatin." So Cantore was
22 teaching 60 wasn't enough. If you read Cantore and the art as a whole,
23 people were saying use 85. And that's the Ychou reference that I mentioned
24 a moment ago, which Conroy applied. Conroy then did this study in 2011
25 and everyone talks about FOLFIRINOX as 85 milligrams per meter square.

1 JUDGE CHANG: So this is Judge Chang. I have two questions.
2 Sorry. So, the first question is, how would you address the routine
3 optimization arguments? Because it does seem that there is a range of
4 efficacy and there's a balance between efficacy and toxicity, which I think is
5 relatively well known for chemotherapy, at least based on the record, it
6 seems. So why would not a skilled artisan be able to routinely optimize the
7 dosage of oxaliplatin to the claim dosage amount?

8 MR. CHEN: Yeah. So I will get to the oxaliplatin part, but I want to
9 first remind everybody that this is a four-drug regimen that we're talking
10 about. So this is not the oversimplified version of the world that Petitioner
11 urges, which is just tweaking one dose of one drug. We're talking about four
12 different drugs here. Okay? So, it's not routine optimization in the first
13 instance because of the new drug of liposomal irinotecan. On Slide 34,
14 when asked in this deposition, Dr. Ratain admitted, I'm looking at the first
15 bolded answer on Slide 34, "What's unclear is whether liposomal irinotecan
16 can increase the efficacy of irinotecan. It is just not entirely clear." It goes
17 on, and then I'm looking at the second round of bolded information, "So it's
18 not been proven that this formulation or this schedule of giving irinotecan so
19 to speak is superior than the more conventional historical approach." Is that
20 true as of today? Yes. So there's no reason, no motivation to swap,
21 substitute irinotecan or liposomal irinotecan even based on Dr. Ratain's
22 opinions.

23 Then, we're talking about the other drugs, and there's complexities
24 with respect to the routine optimization or lack thereof. I'm on Slide 43 of
25 our slide deck. And Dr. Oberstein opined that, dose adjustment in the
26 context of a multi-component drug regimen would not be routine

1 optimization because you compromise efficacy with lower doses. And
2 remember, there's four drugs that we're accounting for here. Each
3 component has different pharmacokinetic properties, and multiple changes
4 can cause variable responses. And again, we have four variables here, right?
5 And what Dr. Ratain says, this is clipped on Slide 43 in the bottom clip on
6 the right hand side, he says, "An anti-cancer drugs," I'm skipping ahead,
7 "Given the narrow therapeutic index of the drugs result in unpredictable
8 clinical effects." That's an admission from Petitioner's expert.

9 So I go back to -- if it's okay, I'll go back to motivation where I was
10 going. Counsel a minute ago talked about, I can't remember what word he
11 used, but I think he agrees that the NCCN guidelines are authoritative and
12 pretty influential. So, we all agree on that. The 2015 version of the NCCN
13 guidelines says the preferred treatment is FOLFIRINOX, not modified
14 FOLFIRINOX. Which Dr. Ratain agrees is 85 milligrams per meter square
15 at the time. Despite the toxicity that we're all talking about here that's the
16 preferred treatment.

17 So, when Petitioner says it's the gold standard despite the toxicities,
18 where's the motivation to modify that? Nothing in life is perfect, right?
19 Everything has side effects. There's no motivation to modify when it's the
20 gold standard. Their argument is just hindsight. So now, okay, so some
21 researchers are playing around with different chemotherapy regimens, and
22 what do they do? They do other things. On Slide 24, the most frequent
23 thing is to remove the 5-FU bolus.

24 And then, in Exhibit B of Dr. Oberstein's declaration, this is Slides 26
25 through 31. This is a compilation of both pre- and post-priority date
26 alternative regimens. It is revealing that none of those regimens on all those

1 slides are the claimed regimen that is allegedly so obvious. That is an
2 objective indicator that Petitioner's argument is just hindsight. The fact that
3 they're sitting here arguing it was so obvious, looking at all these regimens
4 that people were tried on. FOLFIRINOX is the gold standard, and all these
5 other regimens, not one of them is the claim regimen.

6 You asked a little bit about liposomal irinotecan. Petitioner points to
7 a couple of references that deal with liposomal irinotecan. We don't hear
8 much about the fact that Ko actually tests liposomal irinotecan, or talks
9 about it, sorry, as a monotherapy non-combination. And then, where does it
10 go with this conclusion? It says, go combine it with gemcitabine. Once
11 again, Petitioner's reading the art with blinders on. And the dosage that they
12 use irinotecan is 120 escalating to 150. Then Saif questions the toxicity
13 issues and whether it's really worth it to explore liposomal irinotecan. And
14 we already talked about Bayever, which Petitioner admitted does not teach
15 oxaliplatin.

16 JUDGE YANG: So counsel, I have another question.

17 MR. CHEN: Yes.

18 JUDGE YANG: Going back to the claim language, it says a human
19 patient. Is it any human patient or some specific type, or is there any
20 limitation or something we should read into?

21 MR. CHEN: Yes, it's a good question because it's a person who has
22 metastatic pancreatic cancer. I'm paraphrasing.

23 JUDGE YANG: And that's the only requirement?

24 MR. CHEN: Well, as we addressed earlier, they're naive to other
25 anti-cancer drugs.

1 JUDGE YANG: Okay. The reason I ask that is because Bayever, as
2 you pointed out, it used 80 or perhaps higher, 120, but for patients
3 homozygous for this one allele, it actually, even the starting dose is 60,
4 correct? Do I understand that correctly?

5 MR. CHEN: So I'm on slide 37 of our presentation where we
6 addressed this point.

7 JUDGE YANG: I was just a little ahead of myself. Okay. Go ahead.

8 MR. CHEN: I'm sorry. So that's a unique situation with that allele,
9 and we submit that that situation is not really a starting dose per se, because
10 they're testing the 60 to see if they can actually tolerate it. But, they say if
11 they tolerate it, now you're escalating the dose. So assuming there's
12 tolerability, then the starting dose is actually higher than the 60. It's almost
13 like a test, so to speak, or a pre-initiation dose, just to make sure that the
14 patient can tolerate it. In any event, there is no teaching of combining with
15 oxaliplatin. And actually, in other cases of toxicity, they teach a further dose
16 reduction to 50 milligrams per meter square.

17 And so what the art is pointing to is on Slide 38, there is nothing in
18 the art that teaches a correlation of the regular irinotecan to the dose of
19 liposomal irinotecan. As Dr. Ratain admitted, there's no indicator even
20 today of the efficacy or the superior efficacy, so to speak, of the liposomal
21 irinotecan. There are pharmacokinetic differences within it and other art
22 likewise points to higher doses of liposomal irinotecan. Chen points to 120
23 and Conroy points to 150.

24 Let me quickly just go through our reasonable expectation of success
25 or lack thereof. Slide 41. Again, it's our position that Dr. Ratain did not
26 submit opinions addressing Board's claim construction on treating with

1 respect to reasonable expectation of success. The second reason is that
2 Petitioner relies on Patent Owner's expectation of success, the clinical results
3 of other regimens like Conroy, it's not relying on the regimens of the
4 claimed invention and nothing about the combination.

5 And the next argument we had addressed briefly is Dr. Oberstein said
6 that the lowering the dose was not routine optimization because of the four
7 different doses and drugs. In fact, the Federal Circuit said in response to
8 Petitioner's result variable argument that in the *Moderna TX* case where
9 variables interacted in an unpredictable or an unexpected way, the
10 combination is not obvious. I would also submit, that you mentioned a
11 moment ago, Bayever had some data. There's only pre-clinical data in
12 Bayever. Dr. Ratain's own publications acknowledge that pre-clinical
13 studies do not generally predict success of clinical trials and that Phase II
14 trials even have a high negative predictive value, but a low positive
15 predictive value. And as we know, pancreatic cancer drugs have a very low
16 success rate.

17 Finally, I would say that Petitioner ignores the unpredictability of
18 clinical effects in combination therapy. There are four drugs with narrow
19 therapeutic windows that we're talking about here that's significant, inter-
20 individual variability, pharmacokinetic variability. And Dr. Ratain points to
21 Ko and Saif to opine that they offer a hope of improving survival. But the
22 Federal Circuit has been clear in that, in the *OSI* case, that hope is not
23 enough in a highly unpredictable way. With that, I'll turn it over to my
24 colleague, Ms. Mattes.

25 MS. MATTES: Good afternoon. I'm going to speak today about
26 unexpected results. So, the question here is, what would a POSA expected

1 from making the four modifications. And as my colleague just explained,
2 the POSA would not have known how all four simultaneous modifications
3 would've impacted toxicity and/or efficacy. And at best, given the numerous
4 dose reductions, the POSA would've expected compromised efficacy. As
5 Dr. Oberstein has opined in this case, a POSA would've expected that
6 reducing oxaliplatin from 85 to 60 would likely reduce toxicity, but
7 would've also had a corresponding reduction in efficacy. And he set forth
8 that opinion in his declaration at Paragraph 306. Sorry. He also, in addition,
9 presented some real-world evidence that confirmed that expectation that
10 modifications to FOLFIRINOX would in fact reduce efficacy. And for that
11 real-world evidence, he pointed to Exhibit 2031, which presented a modified
12 FOLFIRINOX regimen that had lower overall survival rate from
13 FOLFIRINOX, an 8.6-month survival rate versus a 9.2-month survival rate.

14 JUDGE CHANG: So this is Judge Chang. So, I have a question for
15 you. It seems that you're arguing both that the combination changes the
16 changing variables and combination therapy. You just can't predict what the
17 result is going to be. But you're also arguing that a POSA would've
18 expected the claim to, I guess, produce certain results, and that, you know,
19 the combination is unexpected. So how do you square those two things?

20 MS. MATTES: Well, I think it's unexpected because you don't really
21 know what would happen, right? So you are not going to know, based on
22 the modifications you make, what exactly will come out in the clinic. I think
23 there's some evidence to show that when you look at some of these
24 modifications in some instances there's reduced efficacy. In other instances,
25 there's reduced toxicity. But with a new drug like liposomal irinotecan, you

1 would not have an understanding of what would happen. It would be
2 unpredictable, as my colleague said.

3 JUDGE CHANG: Well, if it's unpredictable, then why is the result
4 unexpected? Because you could have expected to have superior efficacy,
5 you could have expected to have less efficacy. So why is that? I understand
6 the argument with respect to reasonable expectation, but not unexpected
7 results.

8 MS. MATTES: Sure. I think here, unexpected results only comes in
9 if the conclusion would be that there would be some kind of expectation in
10 the art for these dose modifications. So if the expectation in the art is that
11 dose reductions do indeed reduce toxicity, the expectation then would also
12 be that they would reduce efficacy. And there are studies that have shown
13 that in one of those studies that Dr. Oberstein pointed to is the study in
14 Exhibit 2031, where you had some reduction to modified FOLFIRINOX
15 regimen. And in fact, in that study, there was a reduction in efficacy.

16 JUDGE MAJORS: Counsel, I think we might be conflating a little bit
17 with the reasonable expectation inquiry, which is simply that a POSA
18 expects what is claimed. And as I read these claims here, there's no specific
19 efficacy or safety endpoint that's pointed to. So maybe you could speak to
20 that.

21 MS. MATTES: I'm sorry, do you mind just repeating your question
22 just to make sure I understand what you're asking?

23 JUDGE MAJORS: Yes. You seem to be saying that the skilled
24 artisan wouldn't have expected the results that you see with NALIRIFOX,
25 but that's sidestepping, in my view, what is required to make out the prima
26 fascia case, which is simply that you have some, as we construed the claim,

1 some de minimis benefit, given the combination that's claimed. In other
2 words, I don't see that the reasonable expectation inquiry is as high as you
3 seem to be suggesting.

4 MS. MATTES: I see. I don't know if that's what I meant to do. So I
5 apologize if that's what I was doing, going back and doing that. I think the
6 point here, and at least the way Dr. Oberstein has presented this, is that in
7 the art at this time in 2015, a POSA would've expected an oxaliplatin dose
8 reduction from 85 to 60 in combination with some of the other proposed
9 modifications that would've -- it would've had some kind of compromised
10 efficacy. And the point is that NALIRIFOX with that framework in mind, it
11 would've been surprising that it delivered comparable efficacy to
12 FOLFIRINOX while delivering substantially improved tolerability. And so
13 that's the perspective that we're coming from here.

14 JUDGE MAJORS: Okay. Thank you.

15 MS. MATTES: Yes.

16 JUDGE MAJORS: Maybe you could speak specifically to the
17 argument and evidence that Patent Owner offered in support of the nexus
18 showing.

19 MS. MATTES: Sure. So in terms of nexus, they contend that nexus
20 has not been established or has been given short shrift. But while Dr.
21 Oberstein may not have used the term nexus, it's clear from his declaration
22 as well as from Dr. Ratain's declaration that the Challenged Claims are co-
23 extensive with the NALIRIFOX regimen. I would direct you to Paragraphs
24 65 through 68 and 102 of Dr. Oberstein's declaration, as well as his
25 testimony in Exhibit 1210 at Page 83, Lines 4 to 25. In that portion of his
26 declaration and his testimony, he clearly explains that the NALIRIFOX

1 regimen is a commercial embodiment of the claims' invention. And I would
2 also point you to Dr. Ratain's declaration where he concedes also that
3 NALIRIFOX is an embodiment of the claims' invention. And that's Exhibit
4 1002 at Paragraph 166.

5 And so in this situation, when you have a commercial embodiment
6 that's coextensive of the claims' invention, there's a presumption of nexus.
7 It's a rebuttable presumption, but there's a presumption of nexus here. And
8 Petitioner has not offered any expert evidence rebutting this presumption.
9 It's purely attorney argument. And our understanding of their argument now
10 is that there's no evidence that the claims' invention is what's providing this
11 unexpected benefit of improved tolerability or comparable efficacy.

12 However, Dr. Oberstein did explain that a person of skill in the art
13 would understand that claims' treatments provide the benefit on the basis of
14 the NAPOLI-3 clinical trial, and in particular that the starting doses, as
15 opposed to subsequent dose modifications, that it was the starting doses that
16 were significant. And we discussed this in our reply, which is Paper 38 at
17 Page 15.

18 JUDGE YANG: Counsel, if I recall correctly, in the NAPOLI trial,
19 counsel for Petitioner points out all the changes in that protocol. So, I
20 understand although perhaps the starting dosages are the same, the method is
21 not the same as claimed; is that right?

22 MS. MATTES: I would say that the method is still the same because
23 the NAPOLI-3 trial, the starting treatment was with the claim doses, and
24 there were subsequent dose reductions. And so even if later on patients
25 received lower doses, that doesn't mean it falls out of the context of the
26 claimed invention. And when Dr. Oberstein was asked these questions, the

1 way he explains how a POSA reads clinical trial results, it's not on a patient
2 by patient basis, it's the population of patients and what that study
3 demonstrates as a whole in context. And he said that clinical trials allow
4 clinicians to derive information from a population that would be relevant for
5 any individual and that a POSA would understand the claim treatments to
6 provide the benefit on the basis of the NAPOLI-3 trial as a whole. And so
7 the arguments that the Petitioner has made, our attorney argument, based on
8 their reading of the NAPOLI-3 protocol, not based on anything that Dr.
9 Ratain or any other expert has said in this case.

10 JUDGE CHANG: Sorry, this is Judge Chang. I do have a question in
11 claim construction. I think both you and your colleague had mentioned that
12 if there was a dose reduction, if the starting dose is within the claim, then it
13 meets the claim limitation. But the claim actually says, I think that it's
14 consisting of, right? Consisting of this particular combination, and it's once
15 every two weeks. So are you saying that if you start at 60 and let's say you
16 move to 40 or move up to 80, still within the claims?

17 MS. MATTES: So I believe the claim language uses the word
18 comprising?

19 JUDGE CHANG: Consisting of.

20 MS. MATTES: Sorry. Is it both? Oh, I see.

21 MR. CHEN: Do you want to take this question?

22 MS. MATTES: Do you mind just repeating the question one more
23 time? Thank you.

24 JUDGE CHANG: Yeah. So I think the claims say a method of
25 treating the patient, the method comprising administering a particular
26 therapy once every two weeks, but the therapy consisting of this particular

1 combination. So both you and your colleagues suggest that if you start at the
2 dose of, let's say 60, and then you either move it up or down, that's still
3 within the claim. And I'm guess I'm wondering whether that is your
4 construction and how that, you know, interacts with the, you know, the
5 preamble consisting that's -- or the consisting language that's related to
6 antineoplastic therapy.

7 MS. MATTES: Right. I would say that that is our construction that
8 the doses listed in the claim are the starting doses and that it would
9 encompass dose reductions from that point afterwards, after you go through
10 the initial round of treatment that you could have dose reductions that would
11 be part of it. So, I'm not sure if that answers your question or not.

12 JUDGE CHANG: Yeah, but okay. So I see what you're saying. I
13 understand this is your construction, but just to make sure I'm clear, it says
14 an antineoplastic therapy to the patient once every two weeks, the
15 antineoplastic therapy consisting of 60, 60, 200, and 2400. And you're
16 saying that even though it says antineoplastic therapy, it has to be once every
17 two weeks, and it consists of this combination, you can change it after the
18 first dose.

19 MS. MATTES: If it's right. If it's necessary, yes, you can. And I
20 think it's because when it says a method comprising, that allows you to go
21 from the starting doses into further dose reductions after the fact.

22 JUDGE YANG: So you're saying --

23 JUDGE MAJORS: Just one follow-up --

24 JUDGE YANG: Go ahead.

25 JUDGE MAJORS: I'm sorry. Just one follow-up question to that,
26 Counsel. So I think what we're maybe getting at here is in order to practice

1 this Claim 1, do you have to administer the recited drug cocktail in precisely
2 those amounts, at least twice, two consecutive times, the first administration
3 and the second administration? Because as Judge Chang was just saying, the
4 way the claim seems to read is you're administering the antineoplastic
5 therapy to the patient once every two weeks, the antineoplastic therapy
6 consisting of, and then it tells you exactly what that is. So my question is,
7 are you really suggesting that all you need to do is give the four drugs in the
8 recited amounts only one time, the very first time?

9 JUDGE YANG: Hold on. I think there is some issues with
10 connection. Let's see if -- you have less than a minute, but I think Judge
11 Chang is having trouble. Let me try to -- can we have the tech trying to get
12 the Judge Chang back online, please?

13 JUDGE MAJORS: One minute.

14 JUDGE YANG: Ms. Reporter, can we go offline, please? Sorry
15 about that. Judge Chang, are you back online?

16 JUDGE CHANG: Yes, I think I'm back online. Can you hear me?

17 JUDGE YANG: Yes. Judge Majors, you too, right? Okay.

18 JUDGE MAJORS: Yes,

19 JUDGE YANG: Do you recall, Judge Chang, when did you drop off?

20 JUDGE CHANG: I think I had just asked a question about the claim
21 construction and how comprising and consisting of the --

22 JUDGE YANG: Okay.

23 JUDGE CHANG: -- language relates to the issue of starting dose.

24 MS. MATTES: And then I believe Judge Majors further clarified it
25 for me. So I'll provide an answer to that, and then I think my time is
26 probably up.

1 JUDGE YANG: Okay. I'll give you, how about two minutes just to
2 go for that?

3 MS. MATTES: Sure. And so, to give you an answer to that
4 question, it's the claim language, obviously, from our perspective, tells you
5 what the starting doses need to be for the regimen, and the Specification
6 seems to make clear that these are the initial doses, and it allows for the fact
7 that these initial doses can be reduced upon, you know, certain events or
8 certain toxicity events as needed in following rounds of administration. And
9 I think we pointed to those parts of the Specification in our Slide 11.

10 JUDGE CHANG: Okay. Thank you.

11 MS. MATTES: And I guess given the time, there's --

12 JUDGE YANG: You don't have to use it.

13 MS. MATTES: That's generous. So I guess, the Petitioner had it -- I
14 was supposed to also to discuss Ground 2, but the Petitioner hasn't raised
15 that during oral arguments. So we're going to rest our arguments on the
16 briefing that's in the case, as well as for Ground 3. Thank you.

17 MR. SUH: Okay.

18 JUDGE YANG: I just want confirm that you reserved ten minutes,
19 right?

20 MR. SUH: Yes, ten minutes. I'm going to try to do this as quickly as
21 possible, Your Honor.

22 JUDGE YANG: Okay.

23 MR. SUH: Okay. So we can go back on the record, Your Honor. So
24 I just want to talk about one point where we -- I believe Judge Yang, you
25 had talked about this particular 60 milligrams per meter square of liposomal
26 irinotecan in Bayever, right? It talks about the fact that this reduced dose of

1 liposomal irinotecan is a starting dose with respect to particular patients that
2 have that UGT mutation, right? So one thing to be very clear about is that
3 the Challenged Claims do not exclude that patient population, right? So the
4 claims actually cover people with this particular genetic mutation. And for
5 people with that genetic mutation, Bayever teaches that you have to provide
6 a starting dose at 60 milligrams, which is the same claim dose for the
7 liposomal irinotecan. I think that's something that wasn't pointed out in
8 Patent Owner's presentation. Quickly going down here.

9 And then, if we could go to Slide 19, this is what, I also believe,
10 Judge Yang, you had actually raised Paragraph 139 of Dr. Oberstein's
11 definition of treating, right? And he says, "When administering treatment to
12 metastatic pancreatic cancer patients, the goal is always that such treatment
13 will have more than a de minimis therapeutic effect or efficacy for that
14 patient. While some patients may not receive a therapeutic benefit, the
15 intention behind any treatment is for such benefit to occur." Right?

16 And that's what Dr. Ratain had stated in the petition with respect to
17 what treatment means. And I believe that's what the Board arrived at as
18 well. So I think we're really dealing with a situation where the Board and
19 both respective experts are all saying the same thing, perhaps maybe in
20 slightly different words. And in addition to that, the board actually instituted
21 this case in its Institution Decision based upon Dr. Ratain's declaration,
22 right? So, if the Board did not think that Dr. Ratain's declaration had
23 enough support to actually show a method of treatment, then I don't think it
24 would've instituted.

25 In any event Dr. Ratain talked about FOLFIRINOX, right? Which
26 was the gold standard. He also talked about liposomal irinotecan through

1 the Ko and the Saif prior art references, which were Phase II and Phase III
2 clinical trials, which did show a method of treatment.

3 And I also want to talk a little bit about claim Slide 16, right? So I
4 think Judge Majors asked on my counterpart, Mr. Chen, a particular
5 scenario whether if subsequent doses were dosed down after the first starting
6 dose, would that fall within the scopes of the claims? And he emphatically
7 said no. Right? So I think this is the first time we've heard, and I will object
8 to this, I believe this is a new argument. That Patent Owner is now taking
9 the position that the Challenged Claims really are limited to just a starting
10 dose. But there's nothing within the actual patent language, which specifies
11 that the claims are only limited to a starting dose.

12 And these examples that Mr. Chen used from the Specification were
13 talked about a starting dose. And you can't limit the claim just solely based
14 upon one example within the Specification. Because as Mr. Chen further
15 acknowledged, the Specification is then replete with other instances of
16 subsequent doses and, in fact, subsequent doses with dose reductions. So
17 there's no way that this claim could be limited to a starting dose because
18 there's no intrinsic support for that, and the intrinsic support is from the
19 language itself, right?

20 And the other thing that I believe Mr. Chen mentioned is that, well,
21 liposomal irinotecan and oxaliplatin, he said that there would be no
22 motivation to combine because they both cause a similar side effect,
23 neutropenia, right? So therefore there would be no motivation to combine.
24 But I will proffer that it's because of that neutropenia, that one would be
25 further motivated to reduce the dose of oxaliplatin if it's going to be, and

1 there was motivation for this, if there was going to be a combination of these
2 two particular drugs, right?

3 And then if we could go to Slide 9 and 10. I'm almost done. I just
4 want to point out, all right. Patent Owner doesn't really talk about the
5 specific language of these references of Ko and Saif, right? Instead, Ko is
6 only talking about combination with gemcitabine. But look what the actual
7 article says. It says, alone or in combination with gemcitabine when talking
8 about it as being part of a combination regimen.

9 So I don't think that was very reasonable for Patent Owner wanted to
10 argue. Same with the Saif reference, right? They talk about toxicity. Saif
11 says it seems logical to test this drug further in the context of FOLFIRINOX.
12 And of course, toxicity is going to be an issue. It's an issue in every single
13 regimen for advanced pancreatic cancer, even groundbreaking ones that are
14 taking place today, which is a difference in clients. Right?

15 And then finally, if I could just talk a little bit about Count 2. Here we
16 are. Yep. So Count 2, right? We have Claim 2, and what Claim 2 has, it
17 relies upon Claim 1, right? So Dr. Ratain doesn't provide an opinion with
18 respect to Claim 2, but the Masi reference on the record and the Ginocchi
19 reference on the record, it taught a modified FOLFIRINOX. This one was
20 called FOLFOXIRI, but it's the same active ingredients, and it showed that
21 irinotecan should be administered prior to oxaliplatin, right? And this was
22 being shown in pancreatic cancer patients as well. That's what Ginocchi
23 says, right? It doesn't talk about two hours, we admit that. But we think that
24 this two-hour difference, that's just something that could be routinely
25 optimized.

1 Claim 7? Claim 7 just gives a particular sequence of the
2 administration, we believe that is fully disclosed in Masi and in Ginocchi as
3 well as in Conroy and Mahaseth. And then finally, Claim 15, this is talking
4 about administering the method where it comprises administering a
5 corticosteroid. There's no dispute that they ever actually discloses in this
6 particular pancreatic cancer regimen of administering a dexamethasone,
7 which is a corticosteroid. So, thank you very much. I'm going to hand it
8 over to my colleague now.

9 JUDGE YANG: All right.

10 MR. TOFT: I'll just raise a couple extra points. To argue that the
11 starting dose, the claims require a starting dose would render Claim 5
12 entirely superfluous, and claims are not supposed to be interpreted as such.
13 With reference to Patent Owner's arguments regarding Slide 37, I think that
14 to testify and say that if they can handle 60, they would go up and that does
15 not suggest the use of 60 of oxaliplatin. The same could be true in reverse.
16 Conroy Protocol and Appendix suggested using 60 milligrams of oxaliplatin,
17 and the Conroy Protocol showed a lot, most patients had to have a reduction.
18 So again, there's motivation to reduce the oxaliplatin, removal of the 5-FU
19 bolus. And the liposomal irinotecan was also taught in the art, as we have
20 argued. And we view all of this as routine optimization.

21 And then lastly, to Judge Major's point, I do think that there's a
22 discrepancy between the Patent Owner's arguments on reasonable
23 expectation of success and unexpected results here. Treatment, if it is more
24 than a de minimis benefit that's all that required. It doesn't require it to be
25 better than FOLFIRINOX, it requires it to have better than no treatment at
26 all. And here the art was, if you look at Slides 43, 44, and 45 of Petitioner's,

1 this is quite clear the argument that none of those had the claim dose. That's
2 a 102 argument, not a 103.

3 JUDGE YANG: All right. Very good. Before Patent Owner comes
4 up for the sur-reply, I am going to give Petitioner a few more minutes. I
5 want to hear about something else, that is Exhibits 1004 and 1017. Those
6 are the subject of Patent Owner's motion to exclude.

7 MR. TOFT: Okay.

8 JUDGE YANG: Yes, I would like to hear from you. You will be
9 arguing on that point?

10 MR. TOFT: Yes.

11 JUDGE YANG: Very good. Four minutes on that. Go for it.

12 MR. TOFT: So, Exhibits 1004 and 1017 are the Conroy Protocol and
13 Conroy Supplemental Appendix respectively. There is no dispute. Conroy
14 Exhibit 1003, there's no dispute that that was publicly accessible. That is not
15 challenged at all. Both experts agree. The protocol and the appendix are
16 both referenced in Conroy. Now, Conroy was published in the New
17 England Journal of Medicine, which is a very well-known and very well-
18 respected publication. And when Conroy Exhibit 1003 was published, it
19 references both the protocol and the supplemental appendix repeatedly. The
20 --

21 JUDGE YANG: I understand that part actually.

22 MR. TOFT: Okay.

23 JUDGE YANG: I also understand you're saying, as originally
24 published, they include links to those two documents.

25 MR. TOFT: They do.

1 JUDGE YANG: I think that Patent Owner is challenging those links.
2 So I'd like you to address those, the broken link and the capture date. I hope
3 you understand what I'm trying to say.

4 MR. TOFT: So I don't think that the links are broken, the links that
5 exist, so the Wayback machine has captured the Conroy protocol, and you
6 can use links that show that the link has been unchanged to today. So the
7 link that you use, if you log on and look at Conroy, that link is the same one
8 that was captured by the Wayback machine in 2013, 2014.

9 JUDGE YANG: But that protocol does not exist in the Wayback
10 machine?

11 MR. TOFT: The Wayback machine did not capture that prior to
12 2013, but the Wayback machine does not capture everything.

13 JUDGE YANG: Okay.

14 MR. TOFT: And the -- so I'll concede that point. But the, again, the
15 links in Conroy that is captured by the Wayback machine are the same as
16 that used today. So again, there's a presumption I think that the Conroy
17 Protocol and Appendix were used. But in addition, Conroy, as Dr.
18 Oberstein and Dr. Ratain testified, the person with ordinary skill would
19 understand that the protocol had to exist prior to the study. That's just
20 something that exists before a study can get underway. So Conroy was, I
21 think, 2005 to 2009 was the study, and 2011 was the publication. And it's
22 very common as I think Dr. Oberstein testified that most major publications
23 like the New England Journal of Medicine require the protocol to be
24 published alongside. And then the supplemental appendix is also usually
25 published. And as I referenced in the motion to exclude opposition there are

1 multiple points headings that are referenced in Conroy Exhibit 1003,
2 multiple times, different headings.

3 It is clear, I think, from reading Conroy that the author of that not only
4 had access to it, but continually referenced a document that existed, and
5 then, again, repeatedly the New England Journal of Medicine stated about,
6 you know, multiple times, here's the supplemental appendix also available
7 on our website. So I think from that there's an indicia that is reliable. I think
8 all Patent Owner is arguing, is, you know, they haven't shown any indicia of
9 unreliability or any evidence that it was not published. It's just a claim that,
10 you know, they'd like us to provide additional information that the Wayback
11 machine did not capture.

12 JUDGE YANG: Very good. Thank you.

13 MR. CHEN: Thank you, judge. I'll be very quick. First, as a
14 procedural matter, we would object to the argument here at the hearing
15 regarding Ground 2, just a moment ago. That was outside the scope of the
16 oral arguments here today. So we would respectfully move to strike that.
17 Regarding the claims and whether or not they're limited to the starting dose,
18 I have to chuckle, I kind of feel like I'm arguing with my spouse or
19 something. We're not arguing that the claims are limited to the starting dose.
20 The question that I was responding to was from Judge Majors, and I believe
21 hypothetical was among other things. If a regimen includes 85 oxaliplatin
22 and is reduced down to 60, that's what I emphatically said, that is not
23 covered within the claims, because the starting dose according to the claims,
24 includes among other things, 60 oxaliplatin.

25 JUDGE YANG: But that if the starting dose is 60 and reduced to 40
26 in the following cycle, that is including --

1 MR. CHEN: We submitted this, Judge. Yeah. Because the same
2 disclosure and the Specification teaches that you can dial down the doses.

3 JUDGE YANG: The Specification is one thing. Plain language of
4 the claim says consisting of, no?

5 MR. CHEN: Right. But it's also open to, you know, there's a
6 comprising before the consisting.

7 JUDGE YANG: But the language consisting of is addressing the
8 antineoplastic therapy, correct?

9 MR. CHEN: I agree with that.

10 JUDGE YANG: Okay. And then Claim 5 later talked about the Days
11 1 to 15 of the 28-day treatment cycle. So it has to include the subsequent
12 administration?

13 MR. CHEN: Does it have to? You think it's -- it can include. The
14 requirement for the claims is you have to have the starting initial dose.

15 JUDGE YANG: But if you don't, then wouldn't you say there is
16 nothing to limit it further to reach Claim 5, no?

17 MR. CHEN: I think one of the few things that we agree on is that
18 there are toxicity events that require adjustments. The difference with the
19 prior art, which is the heart of the invention, is the starting dose among other
20 things, the new drug, etc., etc. But the starting dose is a key distinction
21 between Conroy and invention in particular. The other thing I wanted to say
22 was counsel brought up Bayever again, and that UGT1A1 allele. Dr.
23 Oberstein in his declaration, which is Exhibit 2076, Paragraph 283,
24 addresses this issue, and he explains that for this allele, they received the
25 initial dose of 60, but the dose of liposomal irinotecan is increased to 80 if
26 the patient does not experience any drug-related toxicity after the first

1 administration. So, the real dose in that kind of unique situation is the 80
2 milligrams per meter square. Dr. Ratain did not offer any rebuttal opinion
3 to the contrary on that. Meaning --

4 JUDGE CHANG: Sorry, this is Judge Chang. I do have a quick
5 question about that. When you were discussing Bayever in your initial
6 presentation you said that, well, the 60 is sort of like a tolerability dose.

7 MR. CHEN: Yes.

8 JUDGE CHANG: You had already said -- I believe you had already
9 also said that when the claim says that patient who has not previously
10 received the antineoplastic treatment that's intended to mean that it's a first-
11 line treatment. So I guess my question is, so if you have a starting dose
12 that's higher, why can that be considered a tolerability dose? And that's still
13 a first-line treatment, like the later the second dose. Why wouldn't the first
14 dose be simply considered tolerability dose and then it's still considered a
15 part of, you know, treating a patient that hasn't previously received it?

16 MR. CHEN: Yeah, I think I understand what you're asking. I think
17 because in this case is Dr. Oberstein has said in this declaration, we are
18 looking to really balance efficacy and toxicity, right? Everything is a
19 balance of that. And what Bayever is teaching you is for efficacy purposes,
20 if the patient can go to 80, yes, then that's what the patient should receive.
21 So, you have to factor in the efficacy. I'll just briefly mention Ko and Saif
22 were mentioned again. That was not the claimed regimen, the four
23 components in the specific doses. So that can't be the basis for reasonable
24 expectation success.

25 And, I'll just end with one thing that I've neglected to address before.
26 Counsel makes a big deal about this ASCO interview and video. I believe

1 it's Slide 27 of their presentation. It's very clear, even if you just look at
2 Slide 27 and the portions that were transcribed, Dr. Oberstein was referring
3 to the schedule when he was speaking. Regardless of what Petitioner may
4 try to infer that statement meant, it was made in 2025, ten years after the
5 priority tape. And that's just another example of how Petitioners relying on
6 hindsight for the arguments. Thank you, Judge.

7 JUDGE CHANG: Actually, sorry, I do have one question for you. So
8 I think there was an argument made that Dr. Ratain did not provide an
9 opinion that's consistent with our claim construction. And I just wanted to
10 point you to exhibit, I guess, his declaration, Paragraph 49 where he says,
11 you know, "The claim does not require the treatment regimen to be superior
12 to any other standard treatment simply that POSA would expect that the
13 treatment regimen be superior to no treatment in some regard." So, how is
14 that different from our construction of de minimis effect?

15 MR. CHEN: I guess, I just offer back to his original construction
16 where he said it doesn't require actual efficacy. That's our position. But in
17 any event, he didn't put in a reply declaration, even if you accept that he did
18 opine in some manner applying the Board's claim construction. Many of Dr.
19 Oberstein's opinions on the merits are unrebutted.

20 JUDGE CHANG: Okay. Thank you.

21 MR. CHEN: Thank you. And if my colleague, Ms. Murphy, if you
22 would like her to address the motion to exclude, or if you're --

23 JUDGE YANG: It's up to you. You have four minutes to address that
24 --

25 MR. CHEN: Would you like to address it?

26 JUDGE YANG: -- if you want to.

1 MR. CHEN: Yep. Thank you.

2 MS. MURPHY: Good afternoon. I'll be brief. I'll just address your
3 questions about Exhibits 1004 and 1017. 1004, obviously we object to on
4 two separate grounds. One is that there was not a certified translation
5 provided, and subsequent attempts to cure that deficiency did not cure that
6 deficiency. The second --

7 JUDGE YANG: I have a question about that. This is really my
8 curiosity. So if you click on that link, the New England Journal of
9 Medicine, does it not return the English version? Does it return the French
10 version?

11 MS. MURPHY: It would seem that it links to the French version, but
12 if you click on that link, it doesn't go to any document. And the only
13 evidence that Petitioner is relying on to say that that Exhibit 1004 is
14 authentic is a link provided in a filing specifically Exhibit 1224. And even
15 then, there's nothing to connect the links cited in that document to the actual
16 document, Exhibit 1004, that they're purporting to say is authentic and is a
17 certified translation of an original French language document. So it's our
18 position that that is insufficient to establish authenticity and the exhibit
19 should be excluded.

20 And the same issue exists for Exhibit 1017 as well. They cite to a link
21 to support authenticity. They don't even have a printout of the Wayback
22 machine page that they're talking about. And, I think we cite cases in our
23 papers that show that the Board requires more of a showing. At a minimum,
24 there's a Wayback machine printout and then a declaration by someone with
25 personal knowledge of, for example, the Wayback machine, how it works, or
26 something more than what Petitioner has provided here, which the link

1 doesn't work. And speculation as to the similarity between the addresses.
2 We think that's insufficient. Yep. Thank you.

3 JUDGE YANG: All right. Very good. This case is a very difficult
4 one, and we very much appreciate both sides here giving this presentation.
5 We are going to give you more work to do. The panel find it sufficiently
6 justified to ask for a short briefing on what we have been discussing today.
7 That is whether the claim language is on the starting dose versus subsequent
8 dose. I'm going to talk to my colleagues about this afterwards, but just so
9 you know, we're going to follow-up with either an email or a short order for
10 a five-page simultaneous briefing on that issue. So, we'll give you a more
11 definitive direction, what's the issue we are looking for of that. All right.

12 MR. SUH: Your Honor --

13 JUDGE YANG: Yes.

14 MR. SUH: -- may I just clarify? With respect to the five-page
15 simultaneous briefing, should that be limited, as it should, to just the record
16 on that has already been submitted?

17 JUDGE YANG: Correct.

18 MR. SUH: Nothing new.

19 JUDGE YANG: No new evidence.

20 MR. SUH: Correct.

21 JUDGE YANG: Yes, that's a very good question.

22 MR. SUH: Thank you.

23 JUDGE YANG: All right. As I said, we very much appreciate you
24 coming here today. We learned a lot from both you, and this case is
25 submitted. And after we receive your briefing, we will work on the final
26 decision, and we will issue that in due course. And we are adjourned.

1 Counsel, please stay for the court reporter in case there is any issue with
2 spelling as we want a clean record. Thank you very much for that.

3 MR. SUH: Thank you, Judge.

4 (Whereupon, the above-entitled matter went off the record at 3:14
5 p.m.)

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