

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 _____

3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4 _____

5 CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

6 Petitioner,

7 v.

8 SHANGHAI MIRACOGEN INC.,

9 Patent Owner.

10 _____

11 Case No. IPR2025-00685

12 U.S. Patent No. 10,792,370

13 Title: Antidrug-Drug Conjugate

14

15

16 VIDEOTAPED DEPOSITION OF

17 DJORDJE ATANACKOVIC, M.D.

18 Washington, D.C.

19 Tuesday, April 14, 2026

20 9:19 a.m.

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Deposition of:

DJORDJE ATANACKOVIC, M.D. ,

the witness, was called for examination by
counsel for the Petitioners, pursuant to
notice, commencing at 9:19 a.m., at the law
offices of Sheppard Mullin Richter & Hampton
LLP, 2099 Pennsylvania Avenue, NW, Suite 100,
Washington, D.C. 20006, before Dawn A. Jaques,
CSR, GLR, and Notary Public in and for the
District of Columbia.

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1 A P P E A R A N C E S:
 (continued)

2

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I-N-D-E-X

WITNESS:

PAGE:

DJORDJE ATANACKOVIC, M. D.

Examination by Mr. Chen

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** NO NEW EXHIBITS MARKED **

PREVIOUSLY MARKED EXHIBITS REFERRED TO

EXHIBIT NUMBER: PAGE:

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1 PROCEEDINGS

2 THE VIDEOGRAPHER: Here begins
3 File No. 1, Volume 1, in the deposition of
4 Dr. Djordje Atanackovic. Today's date is
5 April 14th, 2026, and the time is 9:19 a.m.

6 This deposition is being taken at
7 2099 Pennsylvania Avenue, Northwest,
8 Washington, D.C.

9 My name is DeShawn White, I am the
10 videographer, and the court reporter is
11 Dawn Jaques from Gregory Edwards LLC.

12 Counsel, please identify yourselves
13 and state whom you represent, followed by the
14 court reporter administrating the oath.

15 MR. CHEN: My name is Joe Chen
16 from Fox Rothschild. I'm representing
17 Petitioner for this case, joined me by
18 Daniel Choi.

19 MR. QIU: My name is Fangzhou Qiu
20 from the law firm Sheppard Mullin. I'm
21 representing the Patent Owner for this
22 case.

1 THE REPORTER: Will you raise your
2 right hand to be sworn, sir?

3 (The witness was administered the oath.)

4 Whereupon,

5 DJORDJE ATANACKOVIC, M.D.,
6 was called as a witness, after having
7 been first duly sworn by the Notary
8 Public, was examined and testified as
9 follows:

10 EXAMINATION BY COUNSEL FOR THE PETITIONER

11 BY MR. CHEN:

12 Q Okay, let's start it.

13 Doctor, could you state your full
14 name for the record?

15 A Yes. My full name is Djordje
16 Atanackovic.

17 Q So is there anything prevent you to
18 provide complete and truthful testimony today?

19 A No.

20 Q Okay. So I just want to go through
21 some ground rules. So today in a deposition,
22 so if you don't understand my questions,

1 please let me know. I will try to rephrase my
2 question. So if you start answering my
3 question, then I'll assume you understand my
4 answer [sic]. Will that be okay?

5 A Okay.

6 Q Okay. So also try to answer my
7 question verbally because the court reporter
8 need to enter your answer in the record.

9 Would that be okay?

10 A Okay.

11 Q Thank you. And your counsel may
12 object to my questions from time to time.
13 Unless he instruct you expressly not to
14 answer, you still need to answer my question.

15 Do you understand?

16 A Yes.

17 Q Okay, thank you.

18 So I'm going to -- oh, by the way, I
19 notice that you bring some materials with you.

20 What are they?

21 A That's just my declaration and some
22 exhibits that I used for the declaration.

1 Q Okay.

2 A But there's nothing -- I didn't
3 bring anything else, no additional materials
4 that are not mentioned or anything.

5 Q No notes?

6 A No notes.

7 Q Okay. You understand everything you
8 bring to the deposition can be entered as
9 exhibits?

10 A Yes.

11 Q Okay.

12 A Yeah, right.

13 Q We'll go over that later.

14 A Yeah, yeah.

15 Q Yeah. So can I get a copy of the
16 doctor's declaration, please? That's 2027.

17 Counsel?

18 MR. QIU: Thank you.

19 BY MR. CHEN:

20 Q So, Doctor, you recognize this as
21 your declaration, right --

22 A Yes.

1 Q -- Exhibit 2027?

2 A So if you don't mind, actually, I'm
3 going to use this instead of this.

4 Q Oh, that's fine.

5 A Because this is --

6 Q If they are the same, yeah.

7 A They are the same, but --

8 Q Yeah, it's easier to -- you don't
9 have to use a big folder.

10 And then could you -- you know, from
11 now on, if I go through exhibit, I'm going to
12 use the stamped page number on the bottom
13 right corner, right? So sometimes the exhibit
14 has its own page number, but we're going to
15 use the stamp number to avoid confusion here.

16 So I wanted to go to page 49. Okay,
17 directly under paragraph 103, so you see a
18 signature block, and can you confirm this is
19 your signature?

20 A Yes, this is my signature.

21 Q So this declaration is dated
22 January 21st, 2026, right?

1 A Yes, correct.

2 Q Okay. So can you go to
3 paragraph 19, which is on stamped page 10 of
4 your declaration?

5 A Yes.

6 Q Okay. So in this paragraph, so you
7 can see that you site a reference called
8 Tikhomirov-346, Exhibit 2011, right?

9 A Yes, correct.

10 Q Okay, I'm going to give you a copy
11 of Exhibit 2011. Counsel?

12 MR. QIU: Thank you.

13 BY MR. CHEN:

14 Q So in your declaration, you cited a
15 number of exhibits as references.

16 A Mm-hmm.

17 Q Are you familiar with all these
18 references?

19 A Yes.

20 Q Okay. Did you find those
21 references, or counsel find them?

22 A I found them.

1 MR. QIU: Objection, and calling for
2 privileged information.

3 Doctor, I caution you to not reveal
4 privileged communication between you and
5 counsel in answering this question.

6 MR. CHEN: Answer when he object.

7 THE WITNESS: So I would say yes, I
8 provided the vast majority of these
9 references.

10 BY MR. CHEN:

11 Q Okay. So what about this one,
12 Exhibit 2011? Did you find that reference, or
13 your counsel identified this reference?

14 A I don't remember exactly who at that
15 point identified this.

16 Q Okay. Can you go to page 3?

17 A Mm-hmm. So page 3, yes.

18 Q No, Doctor, the stamped page.

19 A Oh, I'm sorry, yeah.

20 Q Okay. Can you go to line 30 on
21 page 3?

22 A Yeah.

1 Q So I'm going to read that.
2 "Considering the efficacy of
3 anti-EGFR therapies in treating patients that
4 overexpress EGFR, the risk associated with
5 severe skin reaction is currently considered
6 acceptable when managed properly. The risk of
7 anti-EGFR therapy-associated toxicity can be
8 reduced by prior administration of
9 anti-histamine, or by administering anti-EGFR
10 antibody at a reduced and less effective
11 dose." Did I read it correctly?

12 A You read that correctly.

13 Q Okay. Did you present this passage
14 of this reference in your declaration?

15 A I'm not sure I presented this exact
16 part of this in my declaration.

17 Q Okay. Did you mention in your
18 declaration that the risk of a severe skin
19 reaction is currently considered acceptable
20 when managed properly?

21 A I'm not sure I mentioned this
22 specific part of this text in my declaration.

1 Q Okay, fair enough. So I'm going to
2 continue reading this next paragraph.

3 THE REPORTER: Can you tell me what
4 page so I can follow along?

5 MR. CHEN: Page 3 still, on page 3.
6 This one over here.

7 THE REPORTER: Okay, thank you.

8 BY MR. CHEN:

9 Q So starting from line 36, "Efforts
10 to improve upon EGFR antibodies are aimed at
11 generating antibodies having even greater
12 affinity for target antigen."

13 Did I read that correctly?

14 A Yes.

15 Q Did you present that passage in your
16 declaration?

17 A I'm not sure I presented this part,
18 this specific part, in the declaration.

19 Q Okay, let's put aside this reference
20 just for a second. I want to go to your --
21 let me see. Okay, can you go to paragraph 34
22 of your declaration? That's on stamped

1 page 17, I believe.

2 A 17, yeah.

3 Q Paragraph 34. So I'm going to read
4 that paragraph, okay?

5 A Mm-hmm.

6 Q "Finally, Patent Owner cited
7 Tikhomirov-346 (Ex-2011) in its Preliminary
8 Response which is the same reference discussed
9 in Tikhomirov's Strategy B4. More
10 specifically, the antibodies of Tikhomirov-346
11 had 'a binding affinity for EGFR that is about
12 10-fold or more weaker than the EGFR binding
13 affinity of cetuximab.'" That's citing
14 Exhibit 2011, okay? That's Exhibit 2011.

15 So pick up that Exhibit 2011 again.

16 So, Doctor, I tried to understand
17 here, when you mentioned that the antibodies
18 of Tikhomirov-346, what antibody are you
19 referring to in 2011?

20 A So we're talking about -- what exact
21 part of this are we talking about?

22 Q I'm talking about the paragraph 34

1 of your declaration, the last line on the
2 page 17. Page 17.

3 A Yeah. Oh.

4 Q Page 17, yeah. So the last line,
5 right? So what you state here is, "More
6 specifically, the antibodies of
7 Tikhomirov-346."

8 So my question is, can you help me
9 understand what other antibodies of
10 Tikhomirov? So you are citing reference --

11 A Yeah, yeah.

12 Q -- Exhibit 2011.

13 A Okay. Well, I think one example
14 could be -- so some of the antibodies that
15 he's mentioning in his materials are the
16 antibodies, for example, shown on page 26 --

17 Q Page 26?

18 A -- or page 27.

19 Q Table 3, right?

20 A Yeah, so that there are different
21 tables showing -- I wouldn't say specifically
22 Table 3, but you were asking -- I think what

1 you were asking is about antibodies showing
2 his assessment of binding affinity, so I think
3 that's what he's doing in Table -- what is
4 it -- Table 4, for example.

5 Q Table 4-1, that's on the lower part
6 of page 26, right?

7 A 26 and 27 as well.

8 Q 27, okay.

9 So I see that at bottom it mentions
10 that 6/LC, right? Do you see that antibody?

11 THE REPORTER: I'm sorry, which one?

12 I couldn't understand.

13 BY MR. CHEN:

14 Q 6/LC, is that one of the antibodies
15 that Tikhomirov, this reference disclose,
16 right?

17 A That's one of the antibodies that
18 they list, yes.

19 Q Okay. All right.

20 Can you go to Figure 4? That's on
21 page 45.

22 A Page 45?

1 Q Yeah. I always refer to the stamped
2 page, okay?

3 A Yeah.

4 Q And then this Figure 4, and then the
5 figure legend actually is on page 6, if you
6 want to take a look, you know, at
7 figure legend on the page 6 for Figure 4.

8 So the Figure 4, the description
9 here is that -- I think it's the second
10 sentence. Let me read, okay?

11 "The ratio of antibody binding to
12 EGFR overexpressing cells" -- and I'm going to
13 skip those numbers -- and then "relative to
14 antibody binding to parental U87MC cells was
15 calculated," right?

16 And then if you go back to page 45,
17 Figure 4, and look at the y-axis. Y-axis,
18 right, is a ratio of binding, right?

19 A Mm-hmm.

20 Q So those antibody has a higher bar.
21 Does that means they have better selectivity
22 against the tumor cell, do you know?

1 A Yeah, what I would say, that's not
2 the case. That's not what this graph shows.

3 Q Okay. What does that show?

4 A Yeah. So again, I mean, I did
5 not -- I only have the information that's
6 within this thing.

7 Q Mm-hmm.

8 A My impression from this is that what
9 they showed is basically just binding
10 specificity -- specific binding to the target
11 in question, to the EGFR.

12 Q Mm-hmm.

13 A So that's all. That's what they're
14 doing. You know, basically what they're
15 doing -- asking is do these antibodies do what
16 they're supposed to do, which is bind to the
17 target EGFR, and that's what this question --
18 what this table answers.

19 Q Table, okay.

20 A I mean, sorry, the figure.

21 Q Okay. Why don't we go back to table
22 then. On page 26 you mentioned that the

1 antibodies listed in Table 4, right?

2 A Yeah.

3 Q Are those antibody like -- let me
4 see, HC1, 3/LC, 4/LC, 5/LC, 31HC/2, 7/LC,
5 6/LC, are all these antibody do what they're
6 supposed to do as you just categorize?

7 MR. QIU: Objection, unclear.

8 THE WITNESS: Well, I'm not sure we
9 are -- well, I can't answer this question
10 using the materials that are in here.
11 I think to some degree, we're comparing
12 apples with oranges.

13 So the one thing, as I said, is
14 supposed to answer the question whether
15 the antibody binds to its target.

16 BY MR. CHEN:

17 Q Mm-hmm.

18 A And this thing answers or addresses
19 a different question. It answers -- addresses
20 a different question.

21 Q Yeah, okay. What I really try to
22 understand is that in your paragraph 34 of

1 your declaration, you mentioned that the
2 antibodies of Tikhomirov-346, which is
3 Exhibit 2011, I tried to understand what you
4 refer to when you say the antibody of
5 Tikhomirov-346, which antibody are you
6 referring to, or what group of antibody are
7 you referring to?

8 A Well, I think I took like the
9 majority of these into account when I went
10 over -- well, that's all I can say, like all
11 the antibodies that he's describing in his
12 materials.

13 Q Okay. So 7/LC is one of them,
14 right?

15 A Yeah, I would -- I don't remember
16 exactly, but I think they could be one of
17 them.

18 Q Okay. What about 6/LC is also one
19 of them?

20 A Could be. I would have to go way
21 back and, you know, read the whole thing
22 basically to remind myself of what exactly

1 which antibodies I was thinking of when I
2 wrote this, you know.

3 Q Mm-hmm. When did you write this
4 declaration?

5 A That was months ago, so ...

6 Q How many months?

7 A I don't remember exactly, but I
8 would say a few months ago, three months ago.
9 What is it, April? Yeah.

10 Q Okay. Okay, let's put aside this
11 exhibit. Okay, Exhibit 1006.

12 Doctor, you've seen this exhibit
13 before, right, Exhibit 1006, what we also
14 refer to as Leanna, right?

15 A Oh, okay.

16 Q You've seen this before, right?

17 A Yes.

18 Q Okay. So I just want you to look at
19 the front page here, and in the middle of the
20 page, you see that the number, like a
21 parentheses number 54, it says "Title."

22 Can you read me that title, please?

1 A You mean this like above Figure 1
2 title?

3 Q Correct. It says "title."

4 A So 54, "Title: ANTIBODY DRUG
5 CONJUGATE (ADC) PURIFICATION."

6 Q So this -- the title is about
7 purification, right, ADC?

8 A Yeah, that's what it implies, I
9 would think.

10 Q ADC purification, right?

11 A Yes.

12 Q Okay. And then I want you to go to
13 page 4 of this reference.

14 A Okay.

15 Q On the top it says "SUMMARY OF
16 INVENTION," right? I'm going to read the
17 first paragraph, okay?

18 "The invention provides effective
19 methods for separating antibody drug
20 conjugates (ADCs) having different drug loads,
21 as well as compositions obtained using such
22 methods. The invention also provides

1 compositions where higher drug load species of
2 ADCs are removed."

3 So it basically says ADC, right?
4 There's no mentioning of Antibody 1, correct?

5 A So in this -- in this it says --
6 this specific part, it does not mention
7 Antibody 1, yeah, that's correct.

8 Q So the first sentence is, "This
9 invention provides effective methods for
10 separating antibody drug conjugates," right,
11 with different --

12 A That's the first sentence.

13 Q Yep, yep. Okay.

14 Can you go to page 7?

15 Okay, in the middle -- I'm going to
16 read like line 18.

17 A Sorry.

18 Q That's page 7, line 18. Let me know
19 you are there.

20 A Page 7, line 18.

21 Q Exactly. That's the --

22 A Yeah.

1 Q Okay, I'm going to read that first
2 sentence, okay?

3 "In one embodiment, the methods and
4 compositions of the invention include an ADC
5 comprising an anti-Epidermal Growth Factor
6 Receptor (EGFR) antibody," correct?

7 A Yes.

8 Q It does not mention Antibody 1,
9 right?

10 A Not in this sentence, no.

11 Q Okay, let's go to page 11, line 20.
12 I'm going to read that entire paragraph
13 starting from line 20, okay?

14 "The term 'anti-EGFR antibody' is
15 meant to refer to an antibody that
16 specifically binds to EGFR. An antibody
17 'which binds' an antigen of interest, [such
18 as] EGFR, is one capable of binding that
19 antigen with sufficient affinity such that the
20 antibody is useful in targeting a cell
21 expressing the antigen. Antibody 1 is an
22 example of an anti-EGFR antibody," correct?

1 A That's what it's saying, yeah.

2 Q Okay. So you agree this paragraph
3 is providing a definition of the anti-EGFR
4 antibody, right?

5 A It's not a complete definition, but
6 it's part of a definition I would say.

7 Q What else can you further define
8 that?

9 A I mean, if you want, I can read the
10 whole -- I have a whole table in my thing
11 where I define like what are the
12 characteristics of an antibody that you can
13 decide.

14 Q Okay.

15 A I mean, affinity, as I'm saying in
16 my declaration, is one of the characteristics
17 of an antibody.

18 Q But for the last sentence of this
19 paragraph, it say, "Antibody 1 is an example
20 of the anti-EGFR antibody."

21 Did I read that correctly?

22 A Yes.

1 Q It's just an example, right? Okay.

2 A Yeah, that's fine.

3 Q And then can you please go to
4 page 83, all the way to 83?

5 A Mm-hmm.

6 Q This is the claims of the
7 Exhibit 1006, Leanna reference. So the
8 independent claim 1, I'm going to read it to
9 you, Doctor. It's on the top, the first line.

10 It says, number 1, "A method of
11 obtaining a composition comprising Antibody
12 Drug Conjugates (ADCs), said method comprising
13 contacting an ADC mixture comprising a drug
14 loaded species of 4 or less," I'm going to
15 skip reading, and then go all the way to the
16 last line, "wherein the ADC comprises an
17 antibody conjugated to an auristatin."

18 So, Doctor, does this claim 1
19 mention anti-EGFR?

20 A Sorry, may I read this again?

21 Q Yes, please take your time to read
22 the entire claim 1, please.

1 A Claim 1.

2 (Witness reading claim 1 to himself)

3 I would say it does not specifically
4 mention EGFR in this section.

5 Q Okay. Does this claim 1 mention
6 Antibody 1?

7 A It does not. I would say it does
8 not mention Antibody 1 by name really.

9 Q Okay, yeah. So this claim 1 is not
10 limited to anti-EGFR ADC, right?

11 MR. QIU: Objection, calls for legal
12 opinion.

13 THE WITNESS: Well, I don't -- I
14 don't know whether it limits the claim to
15 EGFR or not.

16 All I can say is that, from a
17 scientific perspective, it's not talking
18 about.

19 So what the consequences are in
20 terms of legal -- of legal, you know,
21 questions, I cannot determine that. I'm
22 not able to determine that -- determine

1 that, but I can say that it's -- again,
2 what I said before.

3 BY MR. CHEN:

4 Q Right, right. It does not mention
5 anti-EGFR, ADC, does not mention Antibody 1,
6 correct?

7 A Yeah, it does not mention it by
8 name.

9 Q All right, let's go to paragraph --
10 sorry, not paragraph, on page 87.

11 A Okay, go all the way to the bottom
12 of page 87, so the claim 38. It's all the way
13 to the bottom.

14 A 38? Yeah.

15 Q Yeah, let me know you are there.

16 A Okay, Doctor, I'm going to read that
17 claim 38 to you. "A composition comprising
18 ADCs, wherein 70% of ADCs present have a drug
19 loaded species of 4 or less, and wherein the
20 ADC comprises an anti-EGFR antibody and an
21 auristatin." Did I read that correctly?

22 A Yes.

1 Q Okay. So this claim, claim 38,
2 mention anti-EGFR antibody, right?

3 A Yes.

4 Q But it doesn't mention Antibody 1,
5 correct?

6 A No, this specific passage does not
7 mention Antibody 1 by name.

8 Q Okay, that's fair enough.

9 A You know, I have to say one thing.
10 I mean, you're obviously picking individual
11 claims, and I'm just looking for the -- I'm
12 noticing that they're talking about specific
13 antibodies.

14 So again, I'm a scientist. I do not
15 know like in what way are these claims related
16 to -- I cannot -- I can only like answer your
17 question to the point and say, you know --

18 Q Based on your understanding, that's
19 fine.

20 A Yeah. The legal understanding -- so
21 whether this is like -- you know what I mean?
22 Like even if it's not stated, it's implied

1 that this refers to the antibody further up in
2 the claims. That's not something that I can
3 judge on, right?

4 Q Yeah, that's why -- I think that you
5 answered my question. Basically is all I need
6 to know.

7 And then can we go to page 50,
8 please? I apologize. Actually, we need to go
9 to page 26 first.

10 A Page 56 first?

11 Q 26.

12 A 26 first.

13 Q Okay, let's go to line 8, okay,
14 basically the second paragraph on that page,
15 okay? So let me read.

16 "Anti-EGFR antibodies suitable for
17 use in accordance with the present
18 compositions and methods are typically
19 monoclonal and can include, for example,
20 chimeric (e.g., having a human constant region
21 and mouse variable region), humanized, or
22 human antibodies; single chain antibodies; or

1 the like. The immunoglobulin molecules can be
2 of any type," and I'll skip reading of that,
3 "or subclass of immunoglobulin molecule.

4 For example, the anti-EGFR antibody used in
5 the anti-EGFR antibody drug conjugate of the
6 invention may be Antibody 1."

7 Did I read that correctly?

8 A Yes.

9 Q So the last sentence, it says that,
10 for example, right, the anti-EGFR antibody
11 used in the anti-EGFR antibody drug conjugate
12 of the invention may be Antibody 1.

13 It says "may be," right?

14 A Mm-hmm.

15 Q It didn't say "must be," right?

16 A It says "may be."

17 Q "May be," yeah. So the invention is
18 not limited to Antibody 1; is that right?

19 A That's how you could read it, I
20 guess.

21 Q Okay, let's put aside this --
22 actually, you know what, I just remembered I

1 said we'd go to page 51 earlier, so let's go
2 to page 51 of this reference. Page 51.

3 Okay, so example 1 there,
4 I think the -- let me read the title of
5 Example 1 is a conjugation of auristatin
6 vc-MMAE to --

7 A Excuse me, where are we?

8 Q Oh, sorry, page 50, actually, I
9 should say page 50.

10 Page 50, Example 1, right?

11 A Mm-hmm.

12 Q On the top it says, "Example 1:
13 Conjugation of Auristatin vc-MMAE to Anti-EGFR
14 Antibody 1." Did I read that correctly?

15 A Yes.

16 Q So this section, Example 1, describe
17 the conjugation of the payload and the linker
18 to Antibody 1, and then the payload and the
19 linker is a vc-MMAE; is that right?

20 A Yes, I think so.

21 Q Vc is a cleavable linker, right?

22 A Yes.

1 (Reporter requests clarification)

2 BY MR. CHEN:

3 Q So your answer is yes, right,
4 Doctor?

5 A Yes, as far as I remember.

6 Q Okay. MMAE is a cytotoxic agent,
7 right?

8 A It's a payload, yes.

9 Q Okay. Is that vc-MMAE the same as
10 in the BA03 vc-MMAE? I think in your
11 reference -- in your declaration you refer to
12 it as an MRG003. Do you recall that?

13 A Yeah, yeah, yeah, yeah, yeah. Of
14 course I recall, that's --

15 Q Okay.

16 A So it's -- you know, I'm not exactly
17 sure. I would have to go back again to the
18 original data, but I do know that for the
19 BA03, what's described is a cleavable linker
20 and a payload that's relatively similar, I
21 guess at least, to MMAE, yeah.

22 Q If it would help you to recall

1 your -- refresh your memory, feel free to
2 refer to your declaration about the MRG003.
3 We can actually do it now if you want to. I
4 want to make sure you remember.

5 A Yeah.

6 Q Yeah. So, let's see, I think it's
7 on -- I think it's on page 45 of your
8 declaration. That's the paragraph 91 of your
9 declaration.

10 A Yeah.

11 Q Right. And in here, this section I
12 believe you were talking about MYK-3, which is
13 also later called MRG003.

14 Looking at this paragraph, do you
15 remember now that the -- the linker and the
16 payload for the MRG003?

17 A Yes.

18 Q What's the linker?

19 A It's a vc.

20 Q Okay. What is the payload?

21 A MMAE.

22 Q Okay, so let's go back to Leanna

1 reference now. Go back to Example 1.

2 So you agree that the linker used in
3 the Antibody 1 vc-MMAE is the same linker as
4 the BA03 vc-MMAE, also referred to as an
5 MRG003, right?

6 A Well, yeah, as far as I can -- based
7 on the information that I have from this.
8 Obviously, I don't know any like details, but
9 just going by this, the information that's
10 available in this paragraph, I would say
11 probably, yes.

12 Q The payload is the same, right,
13 MMAE?

14 A I have to assume that this is the
15 same. This is the same name. I do not know
16 whether there are any modifications or
17 anything to it, you know, because I would have
18 to look at the methods of everything in detail
19 to determine whether there's any difference
20 really between this MMAE or that MMAE. That's
21 not something that I can tell you, but like
22 overall, it looks like it's a comparable.

1 Q Mm-hmm, okay.

2 So let's go to Example 2, which is
3 on page 52 of Leanna reference again.

4 So this Example 2, it says that
5 "Batch Purification of Antibody Drug Conjugate
6 (ADC) Using a Hydrophobic Resin," right? So
7 if you can quickly go through that.

8 So is that section, Example 2,
9 talking about purification of ADC of something
10 specific, like a drug loading ratio, like DAR,
11 right, drug antibody ratio of --

12 THE REPORTER: I can't understand
13 what you're saying.

14 MR. CHEN: DAR.

15 THE REPORTER: DAR, I got that.

16 BY MR. CHEN:

17 Q Yeah, DAR, Drug Antibody Ratio. DAR
18 stands for, right, Drug Antibody Ratio, and
19 that's somewhere between 2 to 4, right, in the
20 first paragraph of Example 2, right?

21 Doctor, do I understand it
22 correctly?

1 A Well, what's the question?

2 Q My question is try to, you know,
3 make sure I understand -- confirm my
4 understanding.

5 So Example 2 is talking about
6 purification of the ADC of some specific DAR,
7 right? Is that right?

8 MR. QIU: Objection,
9 mischaracterizes the document.

10 THE WITNESS: Yeah, well, with this
11 I have several problems.

12 First of all, I absolutely do not
13 understand in what way this is relevant
14 to my declaration and what I'm saying in
15 my declaration. That's number one.

16 Number two is -- well, to answer
17 that question, which, again, is
18 outside -- I think it's outside of the
19 scope of my declaration to go over
20 purification methods, but, you know, in
21 order to give you a statement, I would
22 have to, I mean, take a very, very

1 detailed look at the methods that they
2 used, what was their goal, and so forth.
3 I cannot give you like a yes-or-no answer
4 to that question.

5 BY MR. CHEN:

6 Q So Leanna is a primary reference
7 cited in the petition?

8 A Mm-hmm.

9 Q And you also provide opinion related
10 to the scope of the disclosure of Leanna, and
11 this is a part of disclosure of Leanna. This
12 is relevant to your opinion, that's why I'm
13 asking you like what really Leanna teaches,
14 and this is a part of what Leanna teaches.

15 So I want to understand whether you
16 understand exactly what Leanna teaches; that's
17 why I'm asking you this question. It's like,
18 you know, what this part of Leanna really talk
19 about, right?

20 MR. QIU: Objection, form.

21 THE WITNESS: Yeah, I don't -- well,
22 again, this is one of the things that she

1 teach -- or they teach in their document.

2 I think it's of -- and if you're
3 asking me, it's of minor relevance, if of
4 any relevance, to the topic that we're
5 discussing or the main questions that I
6 was asked to provide an opinion on, so --

7 And, well, again, I would have to go
8 over this in more detail because it's a
9 minor aspect, and I've had to read a lot
10 of papers and documents, you know, in
11 detail. I do not have all the, you know,
12 minor details readily available right
13 now, you know, so that I can give you a
14 proper answer to your question.

15 BY MR. CHEN:

16 Q Take your time to read to give
17 you -- to help you to refresh your memory, and
18 read through that Example 2 if you want to.

19 And this is not a new reference.
20 This is the primary reference cited in --

21 A Yes.

22 Q -- that you provide opinion on.

1 This is not I give you a random new reference.

2 A No, no.

3 Q So it's relevant, also relevant to
4 your opinion, because in your declaration, you
5 talk about what Leanna teaches, and I'm asking
6 you about what Leanna teaches now, and this is
7 a part of Leanna's disclosure.

8 A Yeah. Well, I still tend to
9 disagree. I don't think that this is a major
10 part of what she teaches -- of what they teach
11 really. But, you know, yeah, I'd be happy to
12 go over this and take a look and then tell
13 you.

14 So the question was -- again, can
15 you repeat the question so that I know what
16 to --

17 Q I just want you to confirm my
18 understanding, Doctor.

19 Am I understanding correctly that
20 this Example 2 was talking about purification
21 of ADC of a specific DAR?

22 That's all I'm asking.

1 A Mm-hmm. Okay, so let me go over
2 this. So I have to look at Figure 1.

3 (Witness reviewing Exhibit 1006.)

4 I would say the method that they
5 describe -- first of all, the purpose is to
6 purify ADCs, that's correct.

7 Whether it was presented -- or it's
8 presented to demonstrate whether ADCs with a
9 specific DAR are preferably --

10 Q No, I didn't ask for that.

11 No, I did not ask for that.

12 MR. QIU: Counsel, I think you
13 should let the witness finish his answer.

14 MR. CHEN: Yeah, go ahead.

15 THE WITNESS: Well, I was about to
16 say that's not specifically addressed in
17 this -- in this statement.

18 BY MR. CHEN:

19 Q That's not my question. I think you
20 confirmed the first part, right? This is
21 about the -- Example 2 is about the
22 purification of ADC of the -- to specific DAR,

1 right?

2 A No, the specific DAR part, I did not
3 confirm that. It's not saying in that that
4 this is a method to be used to enrich for ADCs
5 with a specific DAR, I don't think so.

6 Q Let me read the Example 2 to you
7 then, first paragraph.

8 Okay, so Example 2, starting from
9 line 9 on page 52, "The following example
10 describes batch purification of an ADC
11 (Antibody 1-vc-MMAE), where the resulting
12 purified composition had an average DAR of
13 2.8." Is that a specific DAR, 2.8?

14 MR. QIU: Objection, asked and
15 answered.

16 THE WITNESS: So I don't know what
17 you mean by "specific." I mean, that's
18 one result. It's a number, right? It's
19 one type of DAR, but I don't know what
20 you mean by "specific."

21 BY MR. CHEN:

22 Q By the end of the purification, the

1 method result in an ADC having average DAR of
2 2.8, correct?

3 A That's what it's saying, yes.

4 MR. QIU: Objection, asked and
5 answered.

6 BY MR. CHEN:

7 Q Okay. Can I have Exhibit 2032? The
8 big one. It's a big one.

9 So this is Exhibit 2032 cited in
10 Patent Owner's response.

11 A Okay.

12 Q Okay? So let me know when you are
13 there.

14 So on the first page -- the cover
15 page, sorry, cover page it says LEPU, right,
16 L-E-P-U, BIOPHARMA CO., LTD, correct?

17 A Yes.

18 Q Stock Code: 2157.

19 A Yes.

20 Q It's Global Offering, correct?

21 A Mm-hmm.

22 Q All right, let's go to page 310, the

1 stamped page number. Do you see that?

2 A Yeah.

3 Q Okay. So on --

4 MR. QIU: Counsel, I just want to
5 clarify. So I see some highlighting
6 here. Is that in the original exhibit,
7 or did you --

8 MR. CHEN: It's not. It's not.

9 MR. QIU: Okay.

10 MR. CHEN: Yeah, it basically is not
11 altering anything, just the highlight,
12 and we can -- we can give you one to
13 confirm with the original copy, yeah.

14 MR. QIU: Oh, no, that's fine. I
15 just want to note for the record that
16 Petitioner added highlighting on this
17 exhibit.

18 MR. CHEN: Correct, yeah, for the
19 exhibit, yeah.

20 BY MR. CHEN:

21 Q Doctor, can you take a look at the
22 last page of -- sorry, the second paragraph on

1 this page, and the last sentence, right? I'm
2 going to read that, all right?

3 "In comparison, MRG003 has
4 demonstrated the following competitive
5 advantages:"

6 A Excuse me, can you point me to this?
7 I'm not sure what --

8 Q The second paragraph from the top,
9 the last sentence.

10 A All right. All right.

11 Q Let me read again.

12 "In comparison, MRG003 has
13 demonstrated the following competitive
14 advantages," right?

15 A Yes.

16 Q By the way, do you recognize this
17 company, L-E-P-U?

18 A Yes, I do.

19 Q You know, right?

20 A Yeah, I do. I'm representing --

21 Q Oh, you're representing this
22 company. It's the Patent Owner, right?

1 A Yeah, it's the Patent Owner, yeah.

2 Q Okay, I see. I see.

3 And then I would continue reading.

4 "Uniquely designed to utilize a
5 humanized anti-EGFR [monoclonal antibody], a
6 clinically-validated MMAE cytotoxic payload
7 and a cleavable vc linker.

8 "The three components in MRG003 are
9 carefully designed:

10 "□ The mAb component of MRG003 is
11 a humanized antibody, which has approximately
12 six to sevenfold increased binding affinity to
13 human EGFR, compared with cetuximab. It
14 facilitates rapid internalization of MRG003
15 into tumor cells as demonstrated in our
16 in vitro assays."

17 Do you agree with what Patent Owner
18 says?

19 A That's what they say.

20 MR. QIU: Objection, form.

21 BY MR. CHEN:

22 Q You can answer.

1 A Is the question -- what I said --
2 what I was saying is you read it correctly.

3 That's what I --

4 Q Yeah.

5 A But what's your question?

6 Q My question, do you agree with what
7 Patent Owner says here?

8 MR. QIU: Same objection.

9 THE WITNESS: Yeah, this is -- I
10 can't say I agree with this statement
11 because it does not have all the
12 information that I would -- that if I had
13 to write this, I would add more
14 information, and then I could say yes, I
15 agree with the statement.

16 I think there is some information
17 missing, I think, in this statement.

18 BY MR. CHEN:

19 Q What information are missing?

20 A For example, I mean, that's just one
21 out of many things. I would like to know,
22 you know, what's the binding to, for example,

1 healthy tissues. You know, that's what I
2 would like to know.

3 That's one example. I could give
4 you more, but that's one thing that I would
5 like to know as a scientist versus a lawyer,
6 I think.

7 Q So it says that MRG003 has six to
8 sevenfold stronger binding compared to
9 cetuximab, correct?

10 A Mm-hmm, that's what it's saying,
11 yeah.

12 Q It facilitated rapid
13 internalization, correct?

14 A Mm-hmm. That's what it's saying,
15 yeah.

16 Q Are you aware of that?

17 MR. QIU: Objection, unclear.

18 BY MR. CHEN:

19 Q Are you aware that the stronger
20 binding of BA03, which is the antibody in
21 MRG003, stronger binding compared to
22 cetuximab --

1 A Mm-hmm.

2 Q -- facilitates internalization of
3 the ADC to the cell. Are you aware of that?

4 MR. QIU: Objection, foundation.

5 THE WITNESS: Yeah, I would say -- I
6 mean, that's -- it's a very -- it's a
7 very broad question. So I would need to
8 know like in what setting? What are
9 you -- what are you asking me about
10 really?

11 You know, are you asking me what's
12 the disease setting? What is -- like
13 compared to what? What antibody? What
14 data are you asking me for?

15 BY MR. CHEN:

16 Q I'm asking you can stronger binding,
17 higher binding affinity, result in more
18 internalization?

19 A In principle? That's what you're
20 asking me? It's like can that happen?

21 Q Right.

22 A Can that happen?

1 Q Yeah.

2 A That's your question?

3 Q Can that --

4 A It's a possible outcome.

5 MR. QIU: Let me voice an objection.

6 Objection, calls for specu- --

7 objection, incomplete hypothetical.

8 MR. CHEN: What is that?

9 MR. QIU: Incomplete hypothetical.

10 MR. CHEN: I don't know, what does
11 that mean? Okay.

12 THE WITNESS: Well, again, I would
13 say -- I mean, it's hypothetical, that's
14 true, but, I mean, if you're asking me
15 for just is this possible? Can that
16 happen? It this a possible consequence
17 of increased affinity, that you'll have
18 an increased internalization? Then I
19 would say yes, it's possible.

20 BY MR. CHEN:

21 Q It's possible, right?

22 A It's a possible outcome, you know.

1 Q Did you discuss internalization in
2 your declaration?

3 A Yeah, I discuss internalization.

4 Q Can you point that to me?

5 A Where I discuss internalization?

6 Q Yeah, in your declaration.

7 A Yeah, I can do that.

8 Q Yes, please.

9 A Yeah. I go over all the mechanisms
10 in the first part -- well, let me put this
11 away.

12 Okay, actually, several places where
13 I go over internalization. I mean, I would
14 say --

15 Q Which paragraph?

16 A For starters, I would say when I
17 give an overview of the technology, that's
18 page 4 -- it starts on page 4.

19 Q Let's go through that one by one,
20 please. Page 4, right?

21 A Page 4 to 5.

22 Q Which paragraph?

1 A And the paragraphs are -- well, it
2 starts with paragraph 4.

3 Q Paragraph 4, okay.

4 A Which I think it's important for me,
5 because that's where I'm explaining that this
6 is -- internalization is one of the
7 characteristics of an ADC.

8 Q Give me a second, let me read
9 paragraph 4.

10 So the paragraph says, "Each of the
11 components of an ADC plays an important role.
12 The antibody is primarily responsible for
13 targeting the ADC to a target cell ... a tumor
14 cell, that expresses the corresponding
15 antigen. Once the antibody binds the antigen
16 on the target cell, it may be internalized by
17 the target cell, thereby delivering ..."

18 So you're talking about the antibody
19 function here; is that right?

20 A Mm-hmm.

21 Q Antibody binds to antigen on the
22 target cell, then an ADC internalize, right?

1 A Possibly.

2 Q What do you mean by possibly? You
3 say that here, right?

4 A No, no, may be --

5 Q Internalized.

6 A May be internalized.

7 Q So in what situation doesn't it
8 internalize?

9 A Oh, there are many situations.
10 I don't know if you've ever designed
11 an ADC, but that's always an open question.
12 It depends on many factors whether you have
13 sufficient internalization.

14 Q Okay.

15 A That's an open question.

16 Q Does a cetuximab internalize?

17 A Yes.

18 Q Does a BA03 internalize?

19 A Yes. Yes, it does.

20 Q Does Antibody 1 internalize?

21 A With Antibody 1, I would think so,
22 but I would have to -- but it's not -- I have

1 to stress this again.

2 I mean, this is a difficult process,
3 and it's not easy -- it's not that
4 everybody -- every single antibody
5 internalizes to a similar degree or anything
6 like that.

7 Q No, no, no, I'm not saying it's
8 simple. Of course it's not simple.

9 Let's go to next section you
10 mentioned talking about internalization.

11 A Mm-hmm.

12 Q What paragraph?

13 A Oh, gosh. Well, all the subsequent
14 is also about -- you know, in the end, it's
15 also about internalization, because when you
16 go over a linker, it's not a trivial question.

17 I mean, if you have a linker that's
18 cleavable, then in the worst case, you lose
19 your payload and you'll have less
20 internalization of the payload.

21 So even like outside of just the
22 antibody, you know, the other factors can play

1 a role in the internalization, degree of
2 internalization.

3 Q So internalization is an
4 important -- I try to rephrase what you say,
5 okay? If my understanding is incorrect, let
6 me know.

7 So you are saying that
8 internalization is important for linker
9 cleavage?

10 A No.

11 Q No?

12 MR. QIU: Objection,
13 mischaracterizes testimony.

14 BY MR. CHEN:

15 Q Let me know your understanding
16 again.

17 A I don't --

18 MR. QIU: Sorry, let's try to not
19 talk over each other, yeah, for the court
20 reporter.

21 THE WITNESS: So all I'm saying is
22 that, you know, depending on how you look

1 at internalization, if -- so what you
2 actually mean -- I think that's what you
3 mean -- is internalization of the
4 construct, because that's the goal,
5 right?

6 Like the payload -- you want the
7 payload, not just the antibody. If the
8 payload stays outside of a cell, I mean,
9 and you just have internalization of the
10 antibody, what's that going to help?
11 It's not going to help too much, right?
12 If you have an ADC, you want the payload
13 to be internalized as well.

14 So that's why it's common sense,
15 right, if you lose the payload along the
16 way for some reason, I mean, you won't be
17 able to internalize it even if the
18 antibody internalizes, you know.

19 So I'm just saying there are other
20 factors that can contribute to
21 internalization of the payload and the
22 eventual outcome, you know. So I think

1 that's nothing to really -- it's just
2 relatively common, like, knowledge, I
3 would say.

4 BY MR. CHEN:

5 Q But did you talk about
6 internalization with respect to BA03 in your
7 declaration?

8 I understand, Doctor, this is a
9 background of technology, right?

10 A Yeah.

11 Q But my question is, did you talk
12 about internalization with respect to BA03 in
13 your declaration? If you did, let me know.

14 MR. QIU: Objection, form.

15 THE WITNESS: Well, I would have
16 to -- I would have to go over the whole
17 thing. If you really want me to point
18 you to everything, I would have to go
19 from page to page because, you know, I
20 don't remember the exact place or where.

21 I mean, so one place, I mention it
22 when I gave the overview on the

1 technology, and that's -- obviously,
2 you know, I wouldn't mention it -- if it
3 didn't play a role in this whole
4 question, I wouldn't have mentioned it,
5 so but if you want -- do you want me to
6 go over the whole thing?

7 BY MR. CHEN:

8 Q No, this is your own declaration.
9 This is not a random reference I give you.
10 This is your own declaration.

11 A Yeah.

12 Q You don't remember anything you say
13 in your declaration?

14 A Oh, yeah, I remember everything I
15 say, but I don't remember the exact place
16 where I go over internalization. You know, I
17 can't give you a page right now, but I could
18 do that, you know.

19 Q Spend five minutes. Can you go
20 through your declaration to refresh your
21 memory, and then tell me where you talk about
22 internalization for BA03 then.

1 A So I'm talking -- this is -- well, I
2 would say -- if you look at page 25, and
3 that's paragraph 49, okay, and I think that's
4 important. I just mentioned the quantity --
5 yeah, it's important I think.

6 Q 40 what? 25?

7 A 49.

8 Q 49?

9 A 49.

10 Q Does it mention internalization?

11 A Yes.

12 Q Where is it? I didn't see that, any
13 mentioning of internalization in paragraph 49,
14 48, and 50.

15 A Yeah, no, it doesn't say -- you're
16 correct, it doesn't say, correct, directly
17 mention internalization, but this is the --

18 Q Well --

19 MR. QIU: Counsel, let the witness
20 finish his answer.

21 MR. CHEN: Sure. Sure, sure, sure.

22 THE WITNESS: No, but it is -- for a

1 POSA, I think it would have -- if they
2 read this, I think it would have been
3 clear to them that this is what this is
4 about.

5 So it addresses the question of
6 toxicity, and I've explained before that
7 to -- you know, the linker is part of the
8 process that will determine the degree of
9 internalization.

10 And if this addresses the linker
11 question, which it does, and if it says
12 that's why you have increased toxicity if
13 you have a non-cleave -- a cleavable
14 linker, then this addresses
15 internalization as well.

16 BY MR. CHEN:

17 Q So let me rephrase my question
18 again. Is this paragraph talking about
19 internalization of BA03?

20 MR. QIU: Objection, asked and
21 answered.

22

1 BY MR. CHEN:

2 Q Yes or no?

3 A Yes, it does.

4 Q Where is it?

5 A It does not specifically mention

6 BA03, but it implies BA03.

7 Q Which --

8 A It's of relevance for BA03.

9 Q It's relevant, but where does it
10 mention BA03?

11 A No, it does not mention the name
12 BA03 in this paragraph, but I think it's still
13 of relevance, that's why I'm mentioning it.
14 That's why I'm explaining, you know, the
15 conclusion from this, because I think it's
16 actually of high relevance.

17 Let me just finish this because I
18 was actually pretty sure that I mentioned the
19 internalization somewhere.

20 So I think that the thing is
21 really -- I do not mention -- I could have
22 mentioned internalization more often, but I --

1 my opinion was that, based on the information
2 that I had given in the technical overview,
3 that's something that people would be able to
4 imply.

5 When I, for example, talk about,
6 you know, Leanna's antibody, Antibody 1, and
7 I'm saying, you know, it has this and that
8 characteristics, and that solves -- basically
9 addresses toxicity, then that would imply,
10 you know, that the toxicity occurs because of
11 internalization of the payload. I'm also
12 talking about the payload, so, yeah.

13 Q So let's close that question. So if
14 you cannot find it, let me know. Can you find
15 that in your declaration, your specific
16 discussion about internalization with respect
17 to BA03?

18 MR. QIU: Objection, asked and
19 answered.

20 THE WITNESS: Yeah, I would say it's
21 probably something that I didn't find
22 necessary to specifically include in my

1 declaration.

2 BY MR. CHEN:

3 Q But earlier you testified that
4 internalization is related to linker release
5 the payload, right?

6 MR. QIU: Objection --

7 MR. CHEN: Correct?

8 MR. QIU: -- mischaracterizes
9 testimony.

10 THE WITNESS: No.

11 BY MR. CHEN:

12 Q Then why you did not talk about
13 internalization?

14 A Because I explain -- like in the
15 very beginning, I explain how does an ADC
16 work, right? And that's when I talk about
17 internalization.

18 And then, from then on, after having
19 given an introduction on the technique, that's
20 what the whole purpose of that was, is to give
21 people all the information that they need to
22 understand the relevance of all the

1 subsequent, you know, characteristics,
2 for example, of BA03. So I didn't find it
3 necessary to go back to the mechanism of
4 action again.

5 Q So does internalization relate to
6 safety issue?

7 A It's one of the factors that's
8 related to safety as well, yeah, I would think
9 so.

10 Q But your declaration talk a lot
11 about safety issue --

12 A Yes.

13 Q -- am I right?

14 A Yes.

15 Q But why don't you talk about
16 internalization? Because it's one of the
17 factors you mention.

18 A Well, I think it's -- I think I've
19 answered this several times before.

20 I do explain the basic, you know,
21 mechanisms behind an ADC. I don't think that
22 like at every point where I describe

1 modifications to an ADC I need to go back and
2 describe again, you know, what's the mechanism
3 of action.

4 I thought that this is clear,
5 you know, or should be clear. That's why I
6 didn't mention it again.

7 Q So you did not talk about that
8 internalization with respect to BA03 in your
9 declaration, right?

10 A Well, indirectly I do, yeah.

11 Q What do you mean by "indirectly"?

12 A Indirectly by saying, for example,
13 when I talk about, and it's obviously an
14 important point, is the affinity of the
15 antibody of the BA03. And when I say,
16 you know, this is something that, you know,
17 could lead to toxicity as well.

18 So then in that moment, I talk about
19 the mechanisms behind, you know, an increased
20 affinity. So what mediates -- what are the
21 mediators of increased toxicity?

22 Q So increased affinity, would that

1 result in increased internalization of ADC?

2 MR. QIU: Objection, incomplete
3 hypothetical.

4 THE WITNESS: Yes, I think that's
5 one possible outcome, yeah. I think
6 we've talked about this before, if I'm
7 correct.

8 BY MR. CHEN:

9 Q Yeah. I want to clarify, okay?

10 A Okay.

11 Q I won't revisit that issue, okay.

12 Let's go back to Exhibit 2032 again.

13 MR. QIU: Counsel, I just want to
14 note the deposition has been going for
15 1 hour and 20 minutes.

16 MR. CHEN: Okay.

17 MR. QIU: Maybe you're in a line of
18 questions, but when you finish, maybe you
19 can take a break.

20 MR. CHEN: Let me finish one more
21 question because this is a pending, okay?

22

1 BY MR. CHEN:

2 Q Back to Exhibit 2032.

3 And so, Doctor, can you take a look
4 at the page 310, and the last paragraph, I'm
5 going to read that to you.

6 A Mm-hmm.

7 Q "Based on the foregoing
8 considerations, we believe that the MRG003 has
9 promising potential to expand into clinical
10 indications to include a wider spectrum of
11 cancer types that overexpress EGFR. The
12 safety profile for MMAE-related clinical AE
13 profile is well understood."

14 Did I read that correctly?

15 A Yes.

16 Q Do you agree that the safety profile
17 for MMAE-related clinical AE profile is well
18 understood?

19 MR. QIU: Objection, relevance.

20 THE WITNESS: Yeah, so --

21 MR. CHEN: No. Counsel, I would ask
22 you to refrain from a speaking objection

1 because you provide lots of like specific
2 information about the objection that's
3 not allowed.

4 MR. QIU: Counsel, objection to
5 relevance is explicitly allowed on the
6 Trial Practice Guide.

7 MR. CHEN: I think it's only
8 objection to form is allowed.

9 MR. QIU: Do you want to go off
10 record and we can look at it?

11 MR. CHEN: For the time being,
12 that's convenient.

13 THE WITNESS: So -- well, that's a
14 very general statement here in this, and
15 I cannot make a statement to this. Yeah,
16 I'm not in a position to judge on
17 whether -- first of all, I mean, what
18 does "well understood" mean? I mean,
19 what does that mean even?

20 I mean, it's -- well, yeah, I know
21 what it says, but to me as a clinician,
22 it's -- it's -- it's -- it's unclear what

1 that means, you know. It's well
2 understood means -- I mean, there is
3 information out there, right?

4 BY MR. CHEN:

5 Q Okay.

6 A But what's the -- what's the
7 conclusion from this?

8 So that just means -- it doesn't
9 really -- to me, it's not of relevance really,
10 I think, you know, so I cannot tell you
11 whether I agree that it was well understood
12 because I don't know what this means really.

13 BY MR. CHEN:

14 Q You understand this document is from
15 Patent Owner, right --

16 A Yeah, I know.

17 Q -- and given to public --

18 A Yes, right.

19 Q -- offering to the investors, right?

20 A Yeah.

21 Q So you don't even understand what
22 does this mean?

1 A Oh, I understand -- I understand the
2 language, but I don't understand the
3 relevance.

4 Q What relevance? Relevance to what?

5 A To what we're discussing, to the
6 value of BA03. I don't understand --
7 you know, I cannot -- first of all, I cannot
8 confirm because I don't know what they're
9 saying really, and I do not understand the
10 relevance to this, you know, topic.

11 Q So your declaration focus a lot
12 about safety, right?

13 A Yes.

14 Q And this one is talking about
15 safety. Why is it not relevant?

16 A Because it's not saying anything,
17 it's not judging anything. It's just saying
18 it's well understood.

19 I mean, what would you make -- if
20 you were a clinician, what would you like do
21 with this statement? I think it's --

22 Q You are -- you are --

1 A It's very broad.

2 Q I'm deposing you.

3 A Yeah. No, I mean -- yeah. Well,
4 I'm asking -- then let me ask myself. What am
5 I supposed to do with this if I'm a clinician?
6 It's just so broad that, you know, I don't
7 think it's very useful.

8 Q What do you think a POSA would
9 understand this sentence?

10 A How would they understand a
11 sentence? I mean, that's -- I would have to
12 speculate. I can't speculate on that.

13 Q The plain meaning of this sentence.

14 A They would think there is
15 information out there on the toxicity of the
16 drug. That's all I can say. I mean, that's
17 what it says. That's what it does. It says
18 it's understood.

19 MR. CHEN: Let's take a break.

20 We'll come back.

21 THE VIDEOGRAPHER: The time is

22 10:46 a.m. We are now off the record.

1 (A break was taken.)

2 THE VIDEOGRAPHER: The time is
3 10:57 a.m. We are now on the record.

4 BY MR. CHEN:

5 Q Doctor, welcome back.

6 How did you prepare for today's
7 deposition?

8 A Well, I -- first of all, I went over
9 my declaration again and again. And then I
10 went over the most important, you know,
11 documents that I'm referencing again, and
12 that's about -- I think that's about it, I
13 would say.

14 Q How many hours did you spend on
15 preparation for today's deposition?

16 A For this deposition?

17 Q Yeah.

18 A I'd have to say -- I don't have a
19 specific number, but for just this deposition,
20 maybe something like 20 to 40 hours. I have
21 no idea. I don't remember.

22 Q Did you talk to your counsel?

1 A Yes.

2 Q For how long?

3 A Oh, my gosh. I don't remember. Out
4 of all of these -- so I did most of it
5 self-preparing. I'd say maybe, if I did a
6 total of 40, say we talked maybe for 6 to
7 8 hours or something like that, I think.

8 Q Who did you talk to?

9 A Oh, it's -- yeah, it's primarily
10 Fred.

11 Q Who else?

12 A That's basically it, if I remember
13 correctly.

14 Q Just Fred?

15 A Yeah.

16 Q So when was that?

17 A On what day?

18 Q Yeah.

19 A Oh, that, I don't know. It was
20 like -- one time was on the weekend, last
21 weekend; and then, I don't remember, the week
22 before maybe. I don't -- I don't have all the

1 dates, you know.

2 Q Do you recall that we had an
3 original deposition date --

4 A Yes, yeah.

5 Q -- on March 26?

6 A Yeah, yeah.

7 Q Did you talk to counsel, your
8 counsel, before that date?

9 A Ever? Did I ever talk to --

10 Q No, right before for preparation of
11 deposition, of course.

12 A Yeah, I think we talked, if I
13 remember, yeah. Yeah, yeah.

14 Q Okay. Can I have Exhibit 2022?

15 So you mentioned that you did review
16 your declaration several times before this
17 deposition, right?

18 A Mm-hmm.

19 MR. CHEN: Okay, counsel.

20 MR. QIU: Thank you.

21 BY MR. CHEN:

22 Q Do you recognize this document?

1 A Yes.

2 Q That's 2022. We're going to refer
3 Crombet -- you reference Crombet in your
4 declaration, right?

5 A Mm-hmm.

6 Q Okay. So can I have my copy?
7 Where's my copy? Oh, here we go, okay.

8 So, Doctor, let me go to the
9 abstract of this reference. The first
10 paragraph of the extract is "Purpose," right?

11 "To evaluate safety and preliminary
12 efficacy of the humanized anti-epidermal
13 growth factor receptor [EGFR] monoclonal
14 antibody h-R3 in combination with radiotherapy
15 (RT) in unresectable head and neck cancer
16 patients"; is that right?

17 A Yes.

18 Q So what is this antibody, monoclonal
19 antibody h-R3? What's this antibody?

20 A So from this, I would say -- well,
21 it says in the sentence it's an anti-EGFR
22 monoclonal antibody.

1 Q Sorry, I need to ask more
2 specifically.

3 A Yeah.

4 Q So is h-R3 nim- -- nimot- -- hold
5 on, let me -- I forgot how to say it.
6 Nimotuzumab, right? Nimotuzumab.

7 THE REPORTER: I'm sorry, I --

8 MR. CHEN: Nimotuzumab.

9 BY MR. CHEN:

10 Q I think in your declaration you
11 mention that this antibody is named
12 nimotuzumab, right?

13 A Yeah.

14 THE REPORTER: I can't understand
15 the word you're saying.

16 MR. CHEN: Nimotuzumab.

17 THE WITNESS: It's in here.

18 MR. CHEN: Yeah, let me go to your
19 declaration to pull that out. Were do
20 you talk about Crombet?

21 THE WITNESS: Crombet is on 13,
22 page 13.

1 BY MR. CHEN:

2 Q 13? 13, okay. Sorry about that.

3 Page 13, right? Here we go. And then
4 where -- I remember you mention about
5 nimotuzumab.

6 A Yeah, and that's 27, like
7 paragraph 27.

8 Q Oh, paragraph 27. This one.

9 A Nimotuzumab.

10 Q Nimotuzumab, yeah.

11 So, Doctor, here is a --
12 nimotuzumab, h-R3, it's an antibody, right?
13 It's not an ADC, correct?

14 A Yeah, I think that's correct.
15 I think that's correct.

16 Q So it's a combination therapy with a
17 radiation therapy, right -- radiotherapy?

18 A Yes, I think that's what they're
19 doing here in this publication, I think.

20 Q So let me see. Going back to
21 paragraph 26, you reference this so-called
22 Crombet's model, right?

1 A Mm-hmm.

2 Q And then paragraph 24 of your
3 declaration, you show a graph from --

4 A Mm-hmm.

5 Q -- which is Figure 3, I believe,
6 from Crombet.

7 Can you -- can you explain to me
8 what is Crombet model you mention in
9 paragraph 26 of your declaration?

10 What do you mean by "Crombet model"?

11 A So, yeah, that's a very good
12 question, actually, because if I remember
13 correctly, I found this whole thing, concept,
14 including this publication, in preparation for
15 my declaration. I came across this
16 publication, and I think, if I remember -- I
17 mean, that was months ago, obviously, but I
18 found -- this is the figure that we're using.

19 Q Figure 3, right, in your
20 declaration, I see that.

21 A Yeah, so that's the figure that
22 we're using. And I think the model -- what I

1 was thinking is, I found interesting, or
2 why -- the reason for why I included this is
3 that they're showing that, contrary to what
4 like common sense would tell you, they found
5 that lower affinity of a certain antibody can
6 be of advantage in terms of tissue
7 selectivity, for example.

8 So that's the model that I'm -- what
9 I'm describing is this idea, that's what I
10 mean by model.

11 Q Right, right.

12 So, of course, I know your
13 conclusion because that's in your declaration.
14 I'm more interested in knowing like what's
15 your -- you know, what's the factual basis
16 that lead to your conclusion, including how to
17 understand, for example, Figure 3.

18 Let's take a look at Figure 3.

19 A Mm-hmm.

20 Q Figure 3, on the top of Figure 3
21 there's an annotation there called "cetuximab
22 would be here. "

1 (Reporter requested clarification)

2 BY MR. CHEN:

3 Q Did you add that notation, or
4 someone else? Do you see that?

5 A Yeah, yeah, yeah, I know what you're
6 talking about. I think that was a -- so I
7 don't remember the details, but I think I was
8 asking when we had the -- so first of all, I
9 found this, and then my question -- my own
10 question was, where would cetuximab be in all
11 this? You know, that's what I would like to
12 know I said, you know.

13 And then I think we added this
14 information to the graph because I think
15 that's something that everybody would like to
16 know. You know, looking at this, that's a
17 very obvious question, I think.

18 Q I guess my question is --

19 A So, yeah, I added it, added this
20 information, you know.

21 Q You added?

22 MR. QIU: Counsel, sorry to

1 interrupt, but I think this may be a
2 clerical error on our part. We did not
3 intend to file an annotated version of
4 this document.

5 MR. CHEN: That's what I want to
6 confirm that. I just want to confirm
7 that annotation is not present in the
8 original paper, correct?

9 MR. QIU: Yeah, we --

10 THE WITNESS: Yeah, no, it's not.

11 BY MR. CHEN:

12 Q It's not, okay. That's all I --

13 A No, no, no. No, yeah.

14 Q Do I understand correctly you added
15 that annotation to that paper?

16 A Yeah, yeah, yes.

17 Q Okay. Understood, okay.

18 So you mentioned that cetuximab
19 would be here. Where is it? "Here" means
20 what?

21 A This is the -- like it's not a
22 dotted line, but this line here.

1 Q The solid line, blue line?

2 A No. I think it's the --

3 Q No, no, I'm talking about the
4 Exhibit 2022. Are you on that?

5 A Oh.

6 Q So you see that annotation?

7 A Yeah, yeah. I'm sorry, I didn't
8 realize that that's what we were --

9 Q Yeah. Do you see that annotation?

10 A Yeah.

11 Q So you added that annotation,
12 correct?

13 A Yeah.

14 Q Okay. Did you add that blue line,
15 blue solid line?

16 A No, I don't think I added the blue
17 solid line.

18 Q It was there?

19 A I think. As far as I remember, it
20 was there, yeah.

21 Q Then what does that blue line mean?

22 A But I didn't -- God.

1 I mean, you know, I don't think --
2 I think what we added is -- I don't know what
3 this -- so what we added is this line.

4 Q The red --

5 A The dotted --

6 Q -- dotted line --

7 A The dotted red line, yeah.

8 Q -- on the Figure 3 in your
9 declaration?

10 A Yes.

11 Q Paragraph 25, on top of that?

12 A Yeah, exactly.

13 Q Okay. You add that line?

14 A That's what we --

15 Q And the boxes on top of that? The
16 boxes.

17 A Yeah, yeah, yeah, right.

18 Q Okay. Okay, I just want to make
19 sure I know exactly what the reference, you
20 know, talk about.

21 A No, exactly, yeah.

22 And I think that was because I

1 just -- again, I just thought that this is
2 more than just data, it's a model, and that's
3 like to make this more, you know, accessible,
4 I think we added this information -- or I
5 added, you know.

6 Q So Crombet, it compared the
7 nimotuzumab with cetuximab, right? Is
8 cetuximab the antibody referred in this paper
9 as an IMC-C225 on page 7?

10 A What? That's actually --

11 MR. QIU: Objection,
12 mischaracterizes document.

13 BY MR. CHEN:

14 Q That's fine. Doctor, go to page 7,
15 right, of -- look at the Crombet paper for
16 now. Sorry about that.

17 A Yeah.

18 Q So look at page 7, okay?

19 A Yes.

20 Q The right column, right?

21 A Yes.

22 Q So the page I'm talking about,

1 "After repeated administrations, h-R3 trough
2 levels matched with mAb doses that were
3 established to be effective in the preclinical
4 models. H-R3 trough levels were similar to
5 those found after the use of IMC-C225 at the
6 doses of --

7 A I'm sorry, where is that again?

8 Q Right column, on the top first --

9 THE REPORTER: At the top.

10 THE WITNESS: Here, okay.

11 BY MR. CHEN:

12 Q The first paragraph I was reading,
13 okay?

14 A Okay.

15 Q All the way to 200/200 mg/m2.

16 Do you see that?

17 A Yeah.

18 Q Okay. So what is the IMC-C25 [sic]?

19 A IMC-C225, right?

20 Q Correct, yep.

21 A I don't know. I'm not sure.

22 Q Let me help you. You say you review

1 your declaration many times.

2 A Yeah. Yeah, yeah, yeah.

3 Q Before this deposition, right?

4 A Yes.

5 Q Okay. But you don't recall

6 IMC-C225? You don't recall that?

7 A No, I don't. I don't. I'm sorry.

8 Q Go to paragraph 23 of your

9 declaration. Can you read like -- yeah, look
10 like paragraph 23 of your declaration, and the
11 one, two, three, four, five -- the fifth line
12 of that paragraph, what it says.

13 A It says IMC -- that's what you mean,
14 IMC?

15 Q That's what you say, right?

16 A Yeah.

17 Q IMC-C225 --

18 A Is cetuximab.

19 Q Is cetuximab, right?

20 A Yeah, yeah, yeah.

21 Q You agree with what you say in your
22 declaration?

1 A Yes, I do, but that's not -- that's
2 something that -- I mean, you know, it's
3 just -- I mean, these are names, and it's just
4 something that, you know, I read hundreds of
5 papers, and it's -- even if I had read this
6 100 times, this could have happened. You
7 know, I'm telling you.

8 Q Okay, so -- it's okay.

9 So my question is, you are
10 comparing -- based on the Crombet model,
11 you're comparing h-R3 with cetuximab, which is
12 also called IMC-C225.

13 Are they from the same trial? The
14 data, are they from the same clinical trial?

15 A So what I am talking about is not --
16 I'm not talking about results of a clinical
17 trial. I'm not talking about the results of a
18 clinical trial.

19 Q The model -- the model, Crombet
20 model in Figure 3, is based on the data from a
21 clinical trial, isn't it?

22 A I do not -- that is -- well, let me

1 think. Are these from a clinical trial? I
2 wasn't totally aware of that.

3 Q Okay.

4 A I don't think it matters really too
5 much, in my opinion, you know, but, you know,
6 I truly think, you know, it's not of
7 relevance.

8 I think the question is, in what way
9 does affinity affect tissue selectivity, or
10 does it affect tissue selectivity?

11 I mean, whether these samples are --
12 yeah, I mean, from a patient -- I mean, from a
13 patient's serum, it's the same antibody.
14 You're not -- you know.

15 Q Page 2 of Crombet paper, right, on
16 left column -- Crombet. Don't look at your
17 declaration yet.

18 A Yes.

19 Q Look at 2022, this Crombet.

20 A Mm-hmm.

21 Q Go to page, 2. Okay, page 2, left
22 column. On the bottom paragraph -- bottom

1 paragraph.

2 A This paper?

3 Q Yep, page 2, left column, okay?

4 So you see the blue box says

5 "PATIENTS AND METHODS," right?

6 A Yeah, yeah.

7 Q So here it tell you where the data
8 come from. The data come from a single-center
9 phase I/II clinical trial, okay? Do you see
10 that? If you want to read it, feel free to do
11 that.

12 So the Crombet model is built --
13 it's built based on the data from the clinical
14 trial using the h-R3 antibody in combination
15 with radiotherapy.

16 A Yeah, yeah, yeah.

17 Q Okay? So my question is,
18 cetuximab -- you compare to cetuximab. Is
19 cetuximab from the same cohort, or are they
20 from the same -- or put a different way, are
21 they from the same clinical trial or from
22 separate clinical trial?

1 A So I would -- well, looking at this,
2 I would think -- I would think they're most
3 likely not from the same clinical trial,
4 unless I have information that's not --
5 absolutely not available. Yeah, you know.

6 Q And look at the Figure 3 again on
7 this paper. That's page 7, right? Page 7,
8 yeah, Figure 3, okay.

9 Can you tell me what's the dosage of
10 h-R3 antibody?

11 A Sorry, Figure 3 again?

12 Q Yeah, Figure 3 on the -- and my
13 question is what's the dose of h-R3? I think
14 it's in the figure legend, right? It's
15 Figure 3.

16 A Yes.

17 Q It depends on the pharmacologic
18 effect on the dissociation constant of the
19 anti-EGFR antibodies. For A, it's a 100 mg
20 dose, and B is 200 mg dose for h-R3, correct?

21 A Yes.

22 Q Okay. So --

1 MR. QIU: Counsel, which page is
2 this?

3 MR. CHEN: Oh, sorry, page 7.

4 MR. QIU: Oh, 7. Okay, sorry.

5 MR. CHEN: I'm talking about
6 Figure 3.

7 MR. QIU: Got it, sorry.

8 MR. CHEN: Figure 3. Figure 3.

9 MR. QIU: Okay.

10 BY MR. CHEN:

11 Q So the dose for the nimotuzumab or
12 h-R3 antibodies is 100 mg and 200 mg, right --

13 A Mm-hmm.

14 Q -- in Panel A and Panel B.

15 And then you look at page 7, on the
16 right-hand side column, right column, can you
17 tell me the dosage for cetuximab or IMC-C225?
18 So what's the dosage for the cetuximab?

19 A Wait.

20 Q So I think it says in that
21 paragraph, right, it's --

22 A Yeah, yeah.

1 Q Use of IMC-C225 at the dose of 200,
2 right, mg/m2, right?

3 A Mm-hmm.

4 Q And then followed by 400, right?

5 A Mm-hmm.

6 Q So you're loading, and then you
7 have --

8 A Yeah.

9 Q -- an increase a little bit.

10 A Yeah.

11 Q So the dosage, are they the same
12 between h-R3 and cetuximab? Are they the same
13 dose or not?

14 MR. QIU: Objection, calling for
15 speculation.

16 MR. CHEN: No, I think we have
17 enough foundation here. I mean, we just
18 established that the h-R3, you use 100 mg
19 or 200 mg, right?

20 And then for cetuximab, we're
21 reading here from the reference you cite
22 in your declaration, the Crombet

1 reference, it says 200/200 mg/m2, and
2 followed by 400/200 mg/m2.

3 My question is simply asking you to
4 confirm are the doses -- doses -- doses
5 for h-R3 and cetuximab the same or
6 different?

7 MR. QIU: Objection, calls for
8 speculation.

9 THE WITNESS: You know, so what
10 you're -- I mean, the thing is you're
11 asking for the dose of cetuximab.

12 Cetuximab is not in here, right, so --

13 BY MR. CHEN:

14 Q No, I just mean you. Not in the
15 curve, but it says in the paragraph I pointed
16 to you, right, in the right-hand side, page 7,
17 and this is a reference you cite.

18 A Yeah, yeah, yeah.

19 Q I did not cite this reference. You
20 found that.

21 A Yes.

22 Q You should know more than I do.

1 I'm asking you the dosage for
2 cetuximab, whether or not that's identical to
3 the dose of h-R3. Simple question.

4 MR. QIU: Same objection.

5 THE WITNESS: Oh, my God.

6 (Witness reading document to
7 himself.)

8 THE WITNESS: Well, based on this
9 information, like what's in here, I would
10 say -- I mean, they don't -- they
11 don't -- I mean, they say loading
12 maintenance. I don't know whether
13 there's more detailed information.

14 You know, just looking at the bear
15 numbers here, I would say they don't
16 look -- it doesn't look as if they were
17 the same.

18 But, you know, again, I don't know
19 what -- like over what like period of
20 time did they do the loading and when did
21 they start the maintenance and all these
22 kinds of things, so I don't have that

1 information. Maybe it's in here, maybe
2 it isn't, but, you know, yeah.

3 BY MR. CHEN:

4 Q So when you rely on the Crombet
5 model, don't you think it's necessary to
6 verify that information, that make sure
7 they're doing a head-to-head comparison?

8 A Yeah, but I don't think -- I mean,
9 the additional cetuximab, that was just -- I
10 don't think that's key to the understanding to
11 the message of Crombet.

12 The Crombet message is just simply
13 that there is a relation between affinity and
14 tissue selectivity, and the fact that
15 unexpected, I think, to some degree, that
16 lower affinity will lead to -- sometimes lead
17 to better test tissue selectivity.

18 Q But don't you think that reliability
19 of the model is very important for you to draw
20 the conclusion?

21 A I don't think it's key to look at
22 the cetuximab, but -- you know, I don't think

1 the cetuximab component is key to the model.

2 I don't think so.

3 Q Well, the paper and most of your
4 declaration compared between nimotuzumab and
5 the cetuximab, right, compared their binding
6 affinity, right?

7 A Yeah.

8 Q And you draw a conclusion that's
9 saying, based on your B4 Strategy, that weaker
10 binding is better.

11 That's your opinion, correct?

12 MR. QIU: Objection, form.

13 THE WITNESS: Well, you know,
14 I think these are two different
15 components. I mean, this is not just
16 one. You're asking me three different
17 questions in combination I'll have to
18 say.

19 You know, I think I've answered the
20 question. I told -- I told you -- I
21 mean, you know, we talked about the
22 cetuximab, and I told you what I think

1 the key message is from this -- from this
2 model from the figure.

3 BY MR. CHEN:

4 Q Right, right. I don't think I asked
5 you about the key information from Crombet.
6 I'm asking you a very simple question.

7 I asked you to tell me whether or
8 not the dose for h-R3 is different or
9 identical from the dose of cetuximab. Very
10 simple yes-or-no answer.

11 MR. QIU: Objection, asked and
12 answered.

13 MR. CHEN: He hasn't answered.

14 THE WITNESS: Oh, yeah, I think I've
15 answered that question.

16 BY MR. CHEN:

17 Q What's your answer?

18 A I mean, I've said that looking by
19 these, like at the bear numbers that are given
20 in here, it doesn't look like the
21 concentration or the dose was the same, but I
22 don't have all the information on how this was

1 administered, over what course of time, you
2 know. So I don't have like all the
3 information I need to give you a perfect
4 answer to that question.

5 Q Okay.

6 A And, well, you know, if you're not
7 interested -- but, you know, I've also said
8 that I don't think that this would change
9 anything; that, you know, if we left cetuximab
10 out here from this figure, I think it would
11 still be a very valuable piece of information.

12 Q Yeah, that's why I'm going through
13 what's the -- how this model actually even
14 develop, right? And we want to kind of look
15 at the information that counsel used to
16 develop that model, and that's why I'm asking
17 you where the data even come from, same trial,
18 different trial, dosage, all kind of stuff.

19 And my follow-up question, Doctor,
20 is that -- look at the Figure 3 again. What
21 are the tissues that this Figure 3 actually
22 draw?

1 A So it's three different types of
2 tissues.

3 Q Uh-huh.

4 A The skin tissue, liver, and tumor
5 tissue.

6 Q Only three tissues?

7 A Mm-hmm.

8 Q But EGFR, based on your opinion, I
9 believe, is expressed everywhere, right?
10 Meaning on a number of tissues, trying to be
11 accurate.

12 MR. QIU: Objection, form.

13 THE WITNESS: So what I'm saying is
14 that EGFR is expressed across different
15 tissues, you know, at different levels,
16 though.

17 BY MR. CHEN:

18 Q Different levels?

19 A Yeah.

20 Q Okay. But why this Figure 3 only
21 address the distribution or binding, whatever,
22 binding of the three tissues?

1 A I think that --

2 MR. QIU: Objection, calls for
3 speculation.

4 THE WITNESS: Yeah, well, I think
5 they could have done more, obviously. I
6 mean, there are more tissues there.

7 But I'm happy to speculate,
8 actually, because I think -- this is pure
9 speculation, but I think they included
10 skin, for example, because that's an
11 important target tissue for toxicities
12 from anti-EGFR antibodies is the skin. I
13 mean, that's a debilitating toxicity in
14 patients who receive these types of
15 agents.

16 So I think that's one reason they
17 included that and not other types of
18 tissues.

19 BY MR. CHEN:

20 Q Skin, right?

21 A Skin.

22 Q What about liver and -- what was the

1 third one? Tumor. Tumor, obviously.

2 A Yeah.

3 Q I don't question you about tumor.

4 Liver.

5 A Liver, I think that's -- well,
6 again, that's even more speculative, but
7 I think that's a toxicity that whenever you --
8 whenever you perform a clinical trial, like as
9 they did or something, one of the key
10 toxicities that you will look at is toxicity
11 of vital organs, such as the liver.

12 So I think -- I would think that
13 that's why they included -- that's probably
14 one of the reasons for why they included the
15 liver, yeah.

16 Q But certainly you have no knowledge
17 that whether they are representative of all
18 tissues, right, where EGFR express, right?

19 A So, yeah, I think it's expressed on
20 several normal tissues. I don't have the
21 exact numbers or anything, but, you know, it's
22 true it's expressed in different normal

1 tissues.

2 Q Right. I guess probably rephrase my
3 question is that this model only represent the
4 characteristics of the binding on the three
5 tissues that describe on this graph, right?

6 A Yeah, that's the three tissues that
7 were included into this analysis as far as I
8 know.

9 Q It does not describe the binding
10 behavior in other tissue, right?

11 A Well, I mean, that's all I can find
12 in this figure is these three tissues.

13 Q Okay, while he's finding that, we
14 can continue on the question.

15 So, Doctor, could you go to page 3
16 of Crombet reference? Page 3, all right.

17 Okay, so this is Figure 1, actually,
18 and there's a box on top, and then there are
19 four — A, B, C, D — equations there. It says,
20 "The four differential equations describe the
21 changes in antibody," and the A stands for
22 plasma, B Tumor, C liver, D skin, right?

1 So, Doctor, did you independently
2 validate this model at all? The Crombet
3 model, to be specific.

4 A Did I validate the model
5 independently?

6 Q Yeah.

7 A Well, I don't understand. What do
8 you mean? Like what's independent? Like how
9 would you do that?

10 Q Validate a model means not just
11 trusting the conclusion. It's actually
12 looking into how the model was developed and
13 what information that author based, and then
14 "independently" means that use that same
15 information, can you come up with the same
16 model and can you draw the same conclusion?

17 So my question is, did you do that?
18 Yes or no.

19 MR. QIU: Objection, form.

20 THE WITNESS: What I did is I went
21 over the publication, all the information
22 that's in there and that was accessible,

1 and then I tried to determine the
2 validity of the results, yeah.

3 BY MR. CHEN:

4 Q Okay. So you looked at the
5 information in this paper?

6 A Mm-hmm.

7 Q And then you tried to understand
8 whether this is a valid analysis or not,
9 right?

10 A Mm-hmm.

11 Q And looking at the equation A, B, C,
12 D --

13 A Mm-hmm.

14 Q Okay, looking at that, did you see
15 the VP? VP is plasma tissue volume, okay?

16 A Mm-hmm.

17 Q VT is a volume for tumor volume, VL
18 is a liver volume, VS is skin volume.

19 Does Crombet actually disclose the
20 parameter of this VP, VT, VL, VS in the paper?

21 MR. QIU: Objection,
22 mischaracterizes the document.

1 BY MR. CHEN:

2 Q It's okay. If you don't see that,
3 that's okay to say that.

4 A Yeah, I see what you're talking
5 about, but I'm not sure whether they disclose
6 all that in their methods. I mean, and
7 that's -- I'll have to say, to be honest with
8 you, that's not how this works, all right?

9 Q That's not my question. I'm asking
10 you a simple question: did Crombet disclose
11 those parameters, VP, VT, VL, VS? It's yes or
12 no. If you don't see that, that's okay.

13 A No, I don't see it in here, but that
14 doesn't mean they didn't disclose it, right?
15 You know that, right?

16 Q I don't understand it.

17 A I can explain to you.

18 There's like to every paper, I don't
19 know the specifics about this one, but number
20 one, like this is a paper that was published
21 in the JCO, which is a leading paper in the
22 field, has an impact factor I think of close

1 to 30.

2 So how this really goes is, to make
3 it for people like me, to give them some
4 confidence in the data, this will go to first
5 the editorial office. They will go over the
6 quality of the data.

7 Then it will undergo peer view, and
8 for a paper like this, this means like leading
9 expert in this particular field. They would
10 question everything, and if there's
11 information missing or if there's something
12 mischaracterized, they would send -- either
13 reject the whole thing or send it back to the
14 author, and they will ask them to add the data
15 that are missing.

16 I'm not objecting -- I'm not trying
17 to -- what I'm saying is like this --
18 publications like this come with some kind of
19 prevalidation -- with extensive validation,
20 actually.

21 So I'm not -- like if your question
22 is do you -- each time you go through a paper,

1 do you independently verify all the data that
2 are in there to make sure they're valid? No,
3 I'm not doing that. I rely on the journal and
4 on the peer review of my peers that this is
5 valid because it's published in a, you know,
6 journal that has extremely high quality
7 criteria. So the answer would be no, I'm not
8 going through all the things in great detail.

9 Number two is -- and that's -- I
10 mean, this is not all the information that's
11 available. I'm guessing -- this is a clinical
12 trial. There must be supplemental material
13 online as well and additional information,
14 maybe even the study protocol, or like more
15 things that you can use to gain a deeper
16 insight into this model.

17 You know, I don't know for this
18 specific one, but I'm pretty sure that there
19 was -- that there is some additional
20 information publicly available.

21 Q But did you look at the supplemental
22 information?

1 A So I do not typically go over all
2 the files, all the original files for every
3 paper. It's not possible, in my opinion.

4 Q But a portion -- I think from your
5 answer -- you know, correct me if I'm wrong --
6 it's basically you haven't validated this
7 model by yourself. That's number one.

8 Number two is that, in this paper
9 alone, it by itself, it doesn't really tell
10 you what VP is, the number -- I mean the value
11 of the VP, VT, VL, VS, right?

12 MR. QIU: Objection, compound.

13 BY MR. CHEN:

14 Q I guess to put another way, question
15 number one is you did not validate the model
16 by itself?

17 A I did not completely revalidate the
18 model by myself, including all the data.

19 Q Then question number two is that
20 this paper, Crombet paper, does not tell a
21 POSA the value of VP, VT, VL, VS, correct?

22 MR. QIU: Objection, asked and

1 answered.

2 THE WITNESS: Yeah. I mean, you
3 know, it's not in here, but it could be
4 somewhere else.

5 BY MR. CHEN:

6 Q Could be somewhere else.

7 A It could be somewhere else.

8 Q Could be in the supplemental
9 material?

10 A Yeah, right, exactly.

11 Sometimes you even have -- I think
12 it's a good question. I think it's a good
13 question, but I think sometimes you'll find
14 something where there was -- it will say
15 additional information is available from the
16 authors upon request, so then you can send
17 them an email and ask them for this
18 information, but that's obviously not
19 something that I can do for every publication.
20 It's not possible. It's not possible.

21 Q Okay, fair enough. I'll just ask
22 you this paper and not -- of course there's a

1 potential source. You may find this
2 information as part of a -- also from
3 supplemental material, but I'm asking this
4 paper because you cite this paper, okay?

5 A Yeah.

6 Q You didn't cite other stuff, right,
7 so that's why. So that's fair enough.

8 Let's go to -- actually, I have one
9 more question for the concentration, right,
10 for the C value, right? A, B, C, D equation,
11 there's a $C_P(t)$, $C_{tumor}(t)$, $C_{liver}(t)$. Looks
12 like it's concentration, right?

13 MR. QIU: Counsel, are you still
14 looking at the Figure 1?

15 MR. CHEN: Yes, Figure 1. Yeah,
16 we're still on Figure 1 on the equations.
17 I'm more specifically focused on the C
18 value. It's concentration.

19 C_P , right, C_{liver} , C_{tumor} , C_{skin} ,
20 okay? So those are concentrations,
21 right?

22 MR. QIU: There's a question?

1 MR. CHEN: Not yet. I'm still
2 thinking.

3 BY MR. CHEN:

4 Q The concentration, do you know how
5 the author convert -- Crombet convert that
6 EGFR copy numbers on the cell into
7 concentration?

8 MR. QIU: Objection,
9 mischaracterizes the document.

10 THE WITNESS: I mean, they're
11 talking about this CT and CB.

12 BY MR. CHEN:

13 Q Yeah.

14 A They're explaining this in the
15 methods, right? That's all I can say.

16 Q Could you point it to me?

17 A CT, like that's a mathematical model
18 for the kinetic binding of the anti-EGFR
19 antibodies, and it's saying, "CT and CB mean
20 total and bound concentration in each time;
21 bound concentration is a function of the
22 antibody dissociation constant which was

1 estimated to be 0.23×10^{-9} M. Numbers of
2 EGFR per cell were assumed to be 106 for the
3 tumor and 104 for the liver and skin.
4 Antibody half-life was 240 hours."

5 Q So you are talking about on page 3
6 on the right-hand side, right?

7 A Yes.

8 Q The column "Mathematical Model for
9 the Kinetic Binding," right?

10 A Yes.

11 Q Okay, I see that now.

12 So this term is related to the
13 number of EGFR per cell, right? So the -- let
14 me read it on that paragraph, so last sentence
15 of that paragraph.

16 So it says "Numbers of EGFR per cell
17 were assumed to be 106 for the tumor and
18 104 for the liver and skin. Antibody
19 half-life was 240 hours," right?

20 A Yes.

21 Q Did I read that correctly?

22 So now I want to give you a copy of

1 the Patent Owner response. Counsel.

2 MR. QIU: Thank you.

3 MR. CHEN: That's Patent Owner's
4 document. You already have that. You've
5 already seen that.

6 BY MR. CHEN:

7 Q So, okay, can you go to page 9 of
8 the Patent Owner Response? Page 9 of the
9 Patent Owner Response. Page 9.

10 A That's the regular number.

11 Q Right. There's no other number.
12 There's no confusion there.

13 A Yeah.

14 Q Okay, so on the top graph, right, so
15 you have -- see a different like size of the
16 bar, different height of the bar?

17 A Mm-hmm.

18 Q Can you tell me what it is? Is that
19 expression on the -- like expression level of
20 EGFR on the different tissues?

21 A So that's what it says in the
22 figure legend, "[E]xpression levels in 27

1 normal tissues."

2 Q Okay, understand. So they have
3 different expression level, right?

4 A Mm-hmm.

5 Q Different copy number EGFR?

6 A Well, I don't know, but --

7 Q It's different expression level.

8 A It doesn't -- it really -- there's
9 no, I mean, proper figure legend, so I don't
10 know what -- like what did they use as a
11 readout assay.

12 Q So you don't know? You haven't seen
13 this? You have not looked at the
14 Exhibit 2007?

15 A Hmm? Yeah, I've looked at this.

16 MR. QIU: Objection,
17 mischaracterizes testimony.

18 BY MR. CHEN:

19 Q Let me ask you again.

20 Did you -- have you reviewed the
21 Exhibit 2007?

22 A Yes, yes, yeah.

1 Q So is that graph based on
2 Exhibit 2007? That's what Patent Owner says
3 here, okay, on the figure legend, right?

4 A Yes.

5 Q This figure is based on
6 Exhibit 2007, page 2, modified to the same
7 y-axis scale in Figure 1. This is from
8 Patent Owner, to remind you.

9 A Yeah.

10 Q So they have different expression
11 level. Which one has the highest expression
12 level?

13 A Like according to this figure, I
14 would say it's placenta maybe.

15 Q Placenta, right?

16 A Mm-hmm.

17 Q And then which one is second?

18 A Well, I would say probably skin.

19 Q Skin is second.

20 And what's the third one?

21 A Oh, my God, it's not easy to say,
22 but I would say --

1 Q Pretty similar, right? Thyroid?

2 A Thyroid maybe.

3 Q Fat?

4 A It's there as well.

5 Q And then as recorded -- I don't know

6 even know how to say. Esophagus, right?

7 A Esophagus, yeah.

8 (Reporter requests clarification)

9 BY MR. CHEN:

10 Q Close, right --

11 A Yeah.

12 Q -- as a third place?

13 So Figure 1 -- Figure 3 again in the

14 Crombet paper. So this model -- this model

15 does not -- does not address the EGFR from

16 placenta, right? Placenta.

17 A No.

18 Q No, right. Probably too obvious,

19 you know. And it does not address the

20 thyroid, right?

21 A Not as far as I can see.

22 Q Does not address fat, right?

1 A No, I don't think so.

2 Q It does not address the esophagus,
3 right?

4 A Right.

5 Q Okay. You can put aside the
6 Patent Owner's -- hold on just a second. Let
7 me ask you.

8 So let's go back to the Crombet
9 paper, and we were previously on this
10 paragraph talking about, you know, the EGFR.
11 "Numbers of EGFR per cell were assumed to be
12 106 for the tumor and 104 for the liver and
13 skin," right?

14 And based on the diagram, Doctor,
15 Figure 1 on Patent Owner Response, did you
16 see, you know, the EGFR expression level on
17 skin and liver are the same, or they are
18 different?

19 A Oh, my gosh.

20 Q So you can see skin is number two,
21 right?

22 A Yeah, yeah.

1 Q We just went through that.

2 Skin is number two, liver is next to
3 the lung, right? So are they the same
4 expression level?

5 A Well, it doesn't look like, but,
6 you know, I don't know whether -- there's no
7 statistical testing or anything, right, so I
8 don't know whether it's significant or not or
9 anything, you know. There is no statistical
10 testing, right? I mean ...

11 Q This is a -- remind you, this is
12 Patent Owner's evidence.

13 A I know, I know, but I'm not sure the
14 purpose is to like really compare like each
15 one of the tissues to a different tissue. I
16 don't think that that was the purpose of this,
17 you know, so that's why I think there's no --
18 but you just asked me that question. You
19 asked me to compare two distinct type of
20 tissues and tell you whether there was like a
21 higher level.

22 So all I'm saying is that was never

1 done for that analysis, so all I can say is
2 describe what I see, you know.

3 Q Yeah. I guess my question is --
4 because here Crombet has assumption that the
5 EGFR is -- you know, number of copy, number of
6 EGFR on the normal cell assumed to be 104 for
7 both skin and liver.

8 A Yeah.

9 Q So my question is, we know from this
10 graph that the expression level is not
11 necessarily the same. They actually have
12 different expression level, but how can the
13 author of Crombet assume EGFR have the same
14 number on liver and skin?

15 A I don't think there's --

16 MR. QIU: Objection, form.

17 THE WITNESS: And I don't --

18 BY MR. CHEN:

19 Q If you want me to rephrase my
20 question, that's fine, yeah.

21 A No, I -- no, I can answer that.

22 I think that's not what they're

1 saying. They're not saying it's the same -- I
2 mean, you'll have to look -- if you look at
3 the -- at the scale, actually what you'll find
4 is they're using a log scale, the one -- I
5 mean, you know, this --

6 Q Log scale here?

7 A Yeah.

8 Q Log scale?

9 A Yeah, right.

10 Q Log scale --

11 A No, not this one. This is not a log
12 scale.

13 Q Which one is a log scale?

14 A I think they're using 10 to the --
15 Crombet is using -- where was it again?
16 104 and 10 to the --

17 THE REPORTER: You're on the wrong
18 page.

19 THE WITNESS: I'm sorry. Yeah, it
20 doesn't matter. So they're using a
21 different scale.

22 I think what the difference is

1 really they're saying -- so what they
2 would say is they're not the same, but
3 they're roughly the same.

4 So this is maybe -- if you look at
5 it, and I don't know whether these are
6 mean values or median values, I would
7 expect maybe median values, but I would
8 say, you know, if you look at this, maybe
9 it has a 50% like increased level on skin
10 versus -- versus --

11 BY MR. CHEN:

12 Q Liver.

13 A -- liver.

14 But they're talking about -- when
15 they talk about, you know, tumor tissues
16 versus healthy -- the few healthy tissues that
17 they selected, they're talking about a whole
18 different range.

19 They're saying this has like 10 or
20 100 times more, the tumor cell, tumor tissue,
21 right? I mean, that's what they're saying.

22 Q I know. Compared to tumor tissue, I

1 understand, 100 fold.

2 A Yeah.

3 Q 106, 104.

4 A You know what I mean?

5 Q No, no, I understand.

6 A So they would say, a POSA or someone
7 like an average person, they would say, well,
8 you know, one thing's for sure, placenta
9 sticks out.

10 But everything else, I mean, there
11 is EGFR there, but they're all relatively
12 comparable, and so I think it's fair -- I
13 still think it's fair -- like if your goal is
14 to compare tumor tissues to healthy tissues
15 to, say, well, tumor tissues on the average,
16 they have like a lot more than most of the
17 normal tissues.

18 Q Right, I understand that, but
19 compare between tumor and normal cell,
20 100 fold, based on Crombet?

21 A Yeah.

22 Q My question is not that.

1 My question is really compare
2 between liver and skin, right? The paper also
3 actually used only a single number, 104, to
4 represent both tissues, but according to
5 Patent Owner's own material here --

6 A Yeah.

7 Q -- they have a different number
8 here, EGFR.

9 A Yeah, so I -- you know, if you asked
10 me -- if you asked me for my opinion, I think
11 that's okay. I think I find this acceptable
12 because there's some variation. Because the
13 variation that I see here, like it takes place
14 on a much different scale versus the
15 comparison of, you know, healthy versus tumor
16 tissue.

17 So I think I would say, well, in the
18 worst case, these two tissues represent
19 examples of one tissue that has slightly below
20 the average, or maybe one that has above the
21 average a little bit, but it's not -- there's
22 no -- biologically, I would say there's no

1 substantial difference really. I think
2 it's --

3 Q But if you look at the highest
4 expression level -- go back to the -- yeah,
5 right, you're looking at the right place.

6 You're looking at the --
7 for example, like a placenta, right, placenta
8 is the highest one. And if you look at the
9 lymph node, right, the lowest one, you're
10 talking about 35-ish to -- you know.

11 A Yeah.

12 Q That's easily how many folds,
13 20-fold, 30-fold, compared between placenta
14 and liver node, right? That's not just
15 twofold difference. There's many fold
16 difference.

17 A Well, you know --

18 MR. QIU: Objection, form.

19 THE WITNESS: No, this is not fair.

20 I mean, this is not a fair comparison.

21 I think if I -- you know, I can
22 explain to you. I mean, these are all

1 epithelial tissues we're talking about.

2 So epithelial tissues express EGFR,

3 normal epithelial tissues.

4 Lymph node, do you know what you

5 have in lymph nodes? Lymphocytes, blood

6 cells. So they don't express EGFR.

7 That's not a mystery; that's a known

8 fact.

9 So I'm not surprised that lymph

10 nodes, such as -- and bone marrow. Bone

11 marrow has no EGFR. So what is that

12 supposed to mean?

13 BY MR. CHEN:

14 Q Doctor, I'm not asking you to

15 explain why they have low expression.

16 A No, I'm just saying it's not a fair

17 comparison. It's not fair to say, well, this

18 is not valid because they included lymph

19 nodes. That's not fair.

20 But I think it would be fair to say

21 placenta, esophagus, like why is there a high

22 expression? You know. And I just said, yes,

1 that's what this shows.

2 Q Yeah.

3 A I just thought that it shows
4 variation at an acceptable level, I think, and
5 this does not diminish the overall conclusion
6 from Crombet when they compare tumor versus
7 two exemplary --

8 Q Yeah.

9 A -- tumor tissue. I still think that
10 that's valid.

11 Q But I'm actually looking to the
12 scientific soundness of the model itself,
13 right? Because if a model makes a number of
14 assumptions, then we have to ask, you know,
15 whether this assumption is justified or not,
16 right? For example, like assumption on the
17 number of EGFR on tumor cell, on the normal
18 cells. And, obviously, Crombet used an
19 unusual number, 104, to represent all the
20 tissue.

21 You know, that's something -- that's
22 why I'm asking you. Obviously, expression

1 level is everywhere, you know, low and high,
2 and that assumption doesn't seem like
3 justified, right, because the expression
4 levels vary so much across different tissue.

5 A I'm not -- I'm not like signing
6 this -- like off on this opinion. I do not
7 think there's like substantial variation
8 across.

9 I mean, what my conclusion would be
10 from this is when there's significant
11 expression all over the place on all
12 epithelial tissues, and there's some
13 variation, but --

14 Q Yeah.

15 A It's not -- it wouldn't change my
16 conclusion from these data.

17 Q Sure, sure, sure. I understand why
18 you cited that to support some of your
19 opinion, but sometimes that evidence can tell
20 different story. That's why I'm saying, okay?

21 A I don't think that's the case here,
22 that's all I can say.

1 Q Well, okay, we can -- we can agree
2 to disagree, right?

3 And then the last sentence, antibody
4 has a half-life of like 240 hours.

5 A Mm-hmm.

6 Q Thus, h-R3 and cetuximab have the
7 same half-life, do you know?

8 A No, I don't know.

9 Q You don't know, right? So it's not
10 an assumption that -- assuming that both h-R3
11 and cetuximab have the same half-life,
12 240 hours?

13 MR. QIU: Objection, form.

14 BY MR. CHEN:

15 Q Correct?

16 A Is that what their --

17 Q Yeah, you can look at it again.

18 The last sentence of that paragraph
19 say, "Antibody half-life was 240 hours,"
20 right? So you don't know.

21 A No. Well, again, that's something
22 that I'm not sure.

1 If you ask me, I would think that
2 that's something, again, that the peer
3 reviewers would have insisted on, on some, you
4 know, clarification on that. I don't think
5 that a paper in JCO will let that go. You
6 know, I don't think so, but, you know.

7 Q But I guess if you want to,
8 cetuximab half-life is well known, right?

9 A Mm-hmm.

10 Q Nimotuzumab is also well known, has
11 a half-life. People can check to see whether
12 there actually is 240 hours on that?

13 A Yes.

14 Q Okay. And then I want you to go to
15 page -- let me see -- yes, page 6 of Crombet
16 reference again, and look at the right column.

17 Do you see that, the right column?

18 Yeah, right.

19 A Page 6?

20 Q Yeah, the right column. Yeah, you
21 are there, correct.

22 A Okay.

1 Q And then the second -- the bottom
2 paragraph there, right? Do you see that?

3 A Yes.

4 Q So let me read.

5 "This different (and favorable)
6 toxicity profile of h-R3 deserves careful
7 discussion. In comparison with IMC-C225,
8 which is the anti-EGFR antibody most widely
9 evaluated, h-R3 has four main
10 differences: first, it is a humanized antibody
11 with a larger proportion of human sequence;
12 second, it has a lower magnitude affinity to
13 EGFR than IMC-C225; third, it has been
14 obtained by humanizing a murine antibody
15 elicited against EGFR of human placenta (not
16 of cultured cells); and fourth, it has
17 different pharmacokinetic properties."

18 Do you see that? Did I read that
19 correctly, Doctor?

20 A I think I lost track. You don't
21 have to read it again, but can you show me?

22 Q You can read by yourself.

1 A Yeah.

2 Q Yeah, this is on the right column.

3 A On the right column underneath
4 this --

5 Q Page 6. Yeah, page 6, the bottom
6 paragraph, and then continue reading the whole
7 paragraph.

8 A (Witness reviewing) Okay.

9 Q Okay. So Crombet also, when they
10 were talking about the favorable or different
11 toxicity profile of h-R3, it mention four
12 differences between h-R3 and cetuximab, right?

13 The first difference is that h-R3 is
14 a humanized antibody containing more human
15 sequence, right?

16 And second one is it has a lower
17 magnitude affinity to EGFR than compared to
18 cetuximab, right, weaker binding?

19 A Yeah.

20 Q And the third is that it has been
21 obtained by humanizing a murine antibody
22 elicited against EGFR of human placenta, not

1 of cultured cells.

2 And then, fourth, it has different
3 pharmacokinetic properties.

4 Did you consider this disclosure of
5 the Crombet?

6 A Mm-hmm.

7 Q You are aware of that, right?

8 A Yeah, mm-hmm.

9 Q So there are four differences that
10 can contribute to the favorable or different
11 toxicity profile of h-R3 antibody, right?

12 A I would think so.

13 Q Okay. So I want to continue on the
14 paragraph right below that that's on page 7 --
15 page 7, and on the left-hand side.

16 "We speculate," do you see that, the
17 left-hand side, page 7?

18 A Page 7?

19 Q Yep, left-hand side, and then from
20 the top --

21 A "We speculate" --

22 Q Second paragraph.

1 A Yeah.

2 Q Let me know you are there.

3 A Mm-hmm.

4 Q "We speculate that for h-R3,
5 effective EGFR blockade in tumors can be
6 achieved without causing deleterious effects
7 on the skin, because the optimal dose is far
8 lower than the toxic dose. In fact, the
9 mathematical model that we have built predicts
10 that there is an affinity window that can be
11 exploited for EGFR antagonists, and that
12 higher affinity is not necessarily the best."

13 Right, correct?

14 A (Witness nodding head yes.)

15 Q So it says the higher affinity is
16 not necessarily the best.

17 Did it say it encompass a higher
18 affinity is bad, or it didn't say? Did they
19 say it's bad, or is it -- sorry, strike that.
20 Let me repeat that.

21 He only say the higher affinity is
22 not necessarily the best, right?

1 A That's what they're saying.

2 Q It did not say the higher affinity
3 is bad, correct? It did not say -- Crombet
4 didn't say --

5 A No, they're saying it's not the
6 best. That's what they're saying here, right?

7 Q Okay.

8 A I mean, that's all I can say.

9 Q Good. Let's put away this
10 reference. What time is it? Do you want
11 to -- is it noon?

12 MR. QIU: It is noon now. Maybe we
13 can take a lunch break?

14 MR. CHEN: Take a lunch break,
15 that's fine.

16 MR. QIU: Okay.

17 MR. CHEN: How much time do we --

18 THE REPORTER: Do we want to go off
19 the record?

20 MR. CHEN: Okay.

21 THE VIDEOGRAPHER: The time is
22 12:03 p.m. We are now off the record.

1 (Lunch break taken.)

2 THE VIDEOGRAPHER: The time is
3 12:40 p.m. We are now on the record.

4 BY MR. CHEN:

5 Q Welcome back, Doctor.

6 Can you -- you have a copy of your
7 declaration in front of you, right?

8 A Yeah, yes.

9 Q You have a section, Appendix 3,
10 I think, that's on page 114. Can you go to
11 page 114?

12 A Let me put this on these things.

13 Q Yeah. In fact, go to --

14 A 114.

15 Q 113, please.

16 A Yeah.

17 Q You are there, right?

18 A Yes, I think so.

19 Q I'm going to be -- actually, you
20 know, if you go several pages back to 107,
21 107, and I just want to read the title of the
22 Appendix 3.

1 You quote the understanding of law,
2 right?

3 A Mm-hmm.

4 Q Understanding of the law, okay?

5 Now let's go back to 113, page 113.

6 And page 113, the last paragraph, so it's
7 talking about reasonable expectation of
8 success. Let read that.

9 "In order for a claim to be found
10 invalid based upon a modification or
11 combination of the prior art, there must be
12 reasonable expectation that a person of
13 ordinary skill would have successfully
14 modified or combined the prior art to arrive
15 at the claimed arrangement. This does not
16 mean that it must be certain that a person of
17 ordinary skill would have been successful -
18 the law only requires that the person of
19 ordinary skill in the art would have perceived
20 a reasonable expectation of success in
21 modifying or combining the prior art to arrive
22 at the claimed invention."

1 Did I read it correctly?

2 A Yes.

3 Q So the reason I'm looking at this
4 section is that I want to make sure, you know,
5 I understand your understanding of reasonable
6 expectation of success.

7 A Mm-hmm.

8 Q So you are aware that the standard
9 of reasonable expectation of success does not
10 require certainty for success, right?

11 A I think that's correct.

12 Q Okay. So there's no guarantee of
13 success required under this reasonable
14 expectation of success standard, right?

15 A I would think so.

16 Q Okay, I want to confirm that.

17 And then in your standard, you were
18 talking about, especially the last sentence,
19 you were talking about a person of ordinary
20 skill in the art would have perceived a
21 reasonable expectation of success in modifying
22 or combining the prior art to arrive at the

1 claimed invention.

2 So I want to talk about the term
3 "the claimed invention," right? And this
4 term, you also mentioned in the -- let me see,
5 try to find the paragraph you also talk about
6 this term. Give me one second. Yeah,
7 paragraph 37, 37 of your declaration.

8 THE REPORTER: Page 20.

9 BY MR. CHEN:

10 Q Yeah, page 20.

11 Let's go to paragraph 85 for now,
12 paragraph 85. Yeah, sorry about that. I want
13 to come back to the 37 and 38 later on.

14 THE REPORTER: Page 42.

15 MR. CHEN: Page 42, right, yeah.

16 BY MR. CHEN:

17 Q So paragraph 85, immediately above
18 that paragraph 85, there's a subsection of
19 Section VIII. It says, "The claimed invention
20 addresses a long-felt and unresolved need for
21 a clinically viable anti-EGFR ADC," right?

22 Did I read it correctly?

1 A (No audible response)

2 Q Did I read it correctly, Doctor?

3 A Sorry, where are we?

4 Q Yeah, I'm reading the subheading.

5 A The subheading, okay.

6 Q Yeah, heading of the Section VIII.

7 I just read that to you.

8 A Okay, okay. I see it, yeah.

9 Q So I tried to understand what do you
10 mean by the claimed invention? What is the
11 claimed invention?

12 A So the claimed invention?

13 Q Yeah.

14 A I mean, it's my understanding from
15 counsel that that's -- the subject of this
16 invention is the ADC described in my
17 declaration.

18 Q Okay. Can you go to paragraph 37 of
19 your declaration?

20 A Yeah.

21 Q Okay, can you take a look at the
22 paragraphs 37 and 38, and that probably will

1 refresh your memory of the claimed invention.

2 Do you see that?

3 A Yes.

4 Q Okay. So independent claim 1, so
5 what you say here is "which recites an
6 antibody-drug conjugate or a pharmaceutically
7 acceptable salt thereof, comprising an
8 anti-epidermal growth factor receptor antibody
9 covalently linked to a cytotoxic agent via a
10 cleavable linker, wherein the anti-epidermal
11 growth factor receptor antibody comprises a
12 heavy chain and a light chain, wherein the
13 heavy chain has a variable region comprising
14 CDR1, CDR2 and CDR3 having sequences as shown
15 in SEQ ID NOs: 5 to 7, and the light chain has
16 a variable region comprising CDR1, CDR2 and
17 CDR3 having sequences as shown in SEQ ID NOs:
18 12 to 14."

19 And then paragraph 38 of your
20 declaration, you continue saying that the six
21 CDR sequences recited in claim 1 are those of
22 the antibody of BA03, right?

1 A Mm-hmm.

2 Q So this claim is really about the
3 anti-EGFR ADC, and then the antibody is
4 defined by CDR sequences, right, which is the
5 BA03 of CDR sequences; is that right?

6 A Yes.

7 Q Okay. So the claim itself actually
8 covers more than just BA03, right, even though
9 it share the same CDR sequences --

10 A Yes.

11 Q -- with BA03?

12 A Yes, I would think so. Yeah, it's
13 more than just the antibody, yeah.

14 Q Okay. So you have the same CDR
15 sequences as those in BA03, and then you can
16 have different sequences in the framework
17 region, can have different sequences in the
18 Fc region, right?

19 A (Witness nodding head yes.)

20 Q And that can account for millions of
21 different antibodies, right?

22 A Yeah.

1 Q Okay. So for the linker of the --
2 the claim 1 specified that it's a cleavable
3 linker, right?

4 A Yes.

5 Q Okay. Cleavable linker, including
6 the vc linker, yes?

7 A Yes, for example.

8 Q But it also can include other
9 linkers?

10 A Other types of -- yeah.

11 Q -- or any cleavable linker?

12 A Mm-hmm.

13 Q Because the claim didn't really
14 specify what cleavable linker is. It
15 basically only say cleavable linker, right?
16 Can be hundreds of different cleavable linker,
17 right?

18 A I would think so, yeah.

19 Q Okay. And then the claim says that
20 for the payload -- I think the claim says a
21 payload, right, payload -- it says a cytotoxic
22 agent, right? A cytotoxic agent?

1 A Mm-hmm.

2 Q It doesn't specify the cytotoxic
3 agent to be MMAE, right? It include -- it
4 does include MMAE, right?

5 A Oh, that's a good question,
6 actually. You're saying it does not include?

7 Q No, no, no. The question is it
8 does, right? It sounds like it does include?

9 A Oh, the question is does it include
10 MMAE?

11 Q Yeah, does it include MMAE?

12 A I would think so. I would think so,
13 but yeah.

14 Q Okay, yeah. So but the cytotoxic
15 agent, its internal cell, it should include
16 like hundreds of thousands of different
17 cytotoxic agent, like payload, right?

18 A Yeah.

19 MR. QIU: Objection, calls for
20 speculation.

21 BY MR. CHEN:

22 Q So this claimed invention is about

1 the anti-EGFR ADC, correct?

2 A Yes, I think so, yeah.

3 Q Okay. So the claim doesn't say this
4 anti-EGFR ADC has to be clinically successful,
5 right?

6 A The claim, whether the claim says
7 that it has to be clinically successful?

8 Q No, the question is that does the
9 claim say the anti-EGFR has to be clinically
10 successful?

11 MR. QIU: Objection, form.

12 THE WITNESS: Well, I don't
13 understand the --

14 BY MR. CHEN:

15 Q Oh, yeah, let me rephrase. That's
16 okay.

17 A Sorry.

18 Q My question is basically your
19 understanding of the claim 1 of the challenged
20 patent.

21 A Mm-hmm.

22 Q My question is, does the claim 1 say

1 that -- has the language saying that the ADC
2 has to be clinically successful?

3 MR. QIU: Objection, form.

4 THE WITNESS: Well, I would have to
5 check the claim. I'm not sure whether
6 there's any mentioning of clinical --
7 clinical -- I would have to check the
8 text of the --

9 BY MR. CHEN:

10 Q But based on your --

11 A -- patent. Well --

12 Q Bring up the patent, Exhibit 1001.

13 I'll give you the patent, yeah.

14 A Well, I don't know. I don't

15 remember.

16 Q That's okay.

17 A I don't remember what clinical name.

18 Q I'll give you a copy. I will give
19 you a copy to refresh your memory, okay?

20 Counsel, this is the challenged

21 patent.

22 So this is really what the case is

1 about, right, about this patent, about the
2 claims of this patent, right? This is why we
3 are here.

4 And then let's go to the last page,
5 you know, of this patent, and that's on
6 patent -- that's on page 25. Page 25.

7 A Yes.

8 Q If you look, the claim 1 is on the
9 left-hand side, column 33.

10 A Yes.

11 Q Take a look -- can you take a look
12 quickly, and then just let me know whether the
13 claim 1 actually contains language that's
14 specifically saying that the ADC has to be
15 clinically or therapeutically successful.

16 If you don't see it, let me know.

17 A Well, yeah. No, I don't see it.
18 All I see is -- well, I'm just wondering what
19 does "pharmaceutically acceptable," you know,
20 what does that mean anyways? But I don't --
21 the specific term that you mentioned, I can't
22 find it in the -- in the --

1 Q You cannot find it, right? Okay.

2 So the claim does not have the
3 language requiring that the ADC to be
4 therapeutically or clinically successful,
5 right?

6 MR. QIU: Objection, asked and
7 answered.

8 MR. CHEN: Okay.

9 THE WITNESS: Yeah, well, you know.

10 BY MR. CHEN:

11 Q Does the claim have any language
12 saying that the ADC has to be safe?

13 A Again, I mean, pharmaceutically
14 acceptable, I don't know whether that, you
15 know, is intended to include anything like
16 that, like safety or anything, but I can't
17 find the -- I mean, there's no mentioning of
18 safety of the term itself.

19 Q Yeah, pharmaceutically acceptable
20 salt, that's a different thing?

21 A That's probably -- yeah.

22 Q That's a different thing. It's

1 not --

2 A Yeah.

3 Q Yeah. But you don't see that
4 language about safety, right, in the claim 1?

5 A I don't see anything.

6 Q Okay. So I basically want to
7 understand what exactly is the claimed
8 invention here.

9 So the anti-EGFR ADC, the antibody
10 is defined by the CDR of BA03, right? And
11 then the linker is a cleavable linker. And
12 then the cytotoxic agent is not defined, it
13 basically just say cytotoxic agent, that's it,
14 right? You agree?

15 A Yeah, it says cleavable linker, and
16 it defines the variable regions, and it does
17 not specifically talk about the payload.

18 Q Mm-hmm. Okay, that's fine.

19 Okay, so what's the benefit of using
20 cleavable linker in the claim 1?

21 MR. QIU: Objection, calls for
22 speculation.

1 MR. CHEN: He's a -- counsel, he's
2 an expert. I can ask him to speculate
3 because you are expert.

4 MR. QIU: Yeah, you still answer. I
5 just voiced my objection.

6 THE WITNESS: Yeah, right, right,
7 right.

8 Well, I think, you know, one has
9 to -- first of all, I would say one has
10 to -- I think if you ask me what's the
11 benefit of a cleavable linker, I think we
12 first -- I think we would have to talk
13 about what's the relevance or like the
14 consequence of a cleavable -- cleavable
15 versus non-cleavable linker.

16 BY MR. CHEN:

17 Q Sure, yeah, right, yeah.

18 A Right. Do you want me to enumerate
19 on that?

20 Q Yeah, yeah, yeah, please. I do want
21 to hear about the -- why the patent, you know,
22 '370, the challenged patent, decided to choose

1 cleavable linker, yeah.

2 A So that question, I'm not sure --

3 MR. QIU: Objection, calls for
4 speculation.

5 THE WITNESS: Yeah. So that
6 question, I'm not sure --

7 BY MR. CHEN:

8 Q Let me rephrase my question.

9 In general, don't have to be
10 '370 patent, in general, what's the benefit of
11 cleavable linker?

12 A Well, I cannot --

13 MR. QIU: Same objection. Sorry.

14 THE WITNESS: Yeah, I would say -- I
15 would say I cannot -- I can tell you what
16 the characteristics are of consequences.

17 BY MR. CHEN:

18 Q Sure.

19 A I cannot say. I mean, this is,
20 you know, a suggestive question.

21 Q Mm-hmm.

22 A So I would say, in general, the way

1 I look at it is that a cleavable linker
2 basically can lead to cleavage of the payload
3 from the antibody outside of a target cell,
4 and that way, you know, the payload can
5 theoretically be released into the
6 environment, tumor microenvironment or a
7 healthy tissue environment, you know.

8 So I think if you want to say
9 advantage or the, you know, consequence of a
10 cleaved -- of a non-cleavable linker would be
11 that basically the payload would stay attached
12 to the antibody, and it will only be
13 released -- hopefully only be released inside
14 of the target cell. You know, in the
15 lysosomes, for example, it will be processed
16 and released. So I think that's the general
17 biological difference between both.

18 Q So you talk about the cleavable
19 linker. You're talking about the cleavable
20 linker is cleaved, and then the payload,
21 cytotoxic agent, leave the cell, go to
22 surrounding environment.

1 Do you mean the bystander effect?

2 Is it called bystander effect?

3 A Well, yeah, that's one of the things
4 that I mean, you know, and that's one of the
5 consequences, but I don't think that's the
6 only consequences -- consequence --

7 Q Okay.

8 A -- for the cleavable.

9 Q Then the non-cleavable linker
10 doesn't have bystander effect, right?

11 A I would say -- I don't think you can
12 generalize that way. I would say it's
13 probably maybe to a lower degree or something.

14 Q Less likely?

15 A Less likely.

16 Q Okay. So MMAE, right?

17 A Mm-hmm.

18 Q MMAE. Looking at the MMAE mentioned
19 in claim 11 of the patent. Still goes to last
20 page, page 25. So what's -- what is the
21 advantage of MMAE? What's the benefit?

22 MR. QIU: Objection, form.

1 THE WITNESS: Well, first of all, I
2 don't think that I'm saying in my
3 declaration that there's an advantage
4 that that's a preferable -- I think, if I
5 remember correctly, I'm saying that there
6 were a lot of different payloads,
7 cytotoxic agents, available that were
8 very potent at the time.

9 BY MR. CHEN:

10 Q Right now I'm not questioning you on
11 the specific things you say in the
12 declaration. I'm asking you a general
13 question on MMAE. What's the benefit of MMAE?

14 A So, yeah, well, that's why I
15 answered. I don't think I've ever said that
16 there's a benefit of using MMAE over other
17 types of payloads, if that's what you mean. I
18 don't think that that's what I'm saying --
19 that's what I'm saying, so if you ask me that
20 question --

21 Q But you opine in your declaration,
22 you're saying that the unexpected result is

1 associated with ADC that's described in this
2 patent. That's why I'm asking you what's the
3 benefit of MMAE, because the unexpected result
4 you mentioned has MMAE. This is relevant
5 question.

6 A No, I'm not saying it's --

7 MR. QIU: Objection, form.

8 THE WITNESS: -- relevant, but the
9 fact that I'm saying there were
10 unexpected results does not mean that
11 that's related to the MMAE, and I'm not
12 saying that.

13 I'm not -- I'm not -- I'm not
14 proposing that that's based on or not
15 based on the MMAE. That's not what I'm
16 addressing in my opinion.

17 BY MR. CHEN:

18 Q Okay, then it seems we're talking
19 unexpected result, and what exactly do you
20 attribute unexpected result to?

21 A Well, yeah, that's something that
22 I'm explaining in great detail, I think, in

1 the -- and my opinion is, I would say
2 unexpected because of the other
3 characteristics of the, for example, the BA03
4 antibody. That's another component, right,
5 and the linker as well.

6 Q Okay.

7 A So the payload, I'm not sure. I
8 don't think I'm addressing that, and I don't
9 have a very solid opinion on that.

10 Q Okay. I'm going to come back to
11 unexpected result later, but right now let's
12 talk about the reasonable expectation of
13 success. Let's continue working on that. I
14 want you to go to -- let me see. Give me one
15 second.

16 Okay, can you go to paragraph 82 of
17 the -- of your declaration?

18 A 82?

19 Q Yeah, 82. That's on page 40. So
20 let me know you are there.

21 A Yeah.

22 Q Okay. So paragraph 82, here you

1 stated that, you know, the -- let me read this
2 one.

3 "The '370 patent provides a good
4 discussion of factors that a POSA would have
5 considered in forming an expectation as to
6 whether an ADC would have been successful,"
7 okay?

8 What do you mean by "ADC would have
9 been successful"? Do you mean clinically
10 successful or therapeutically successful?

11 MR. QIU: Objection, form.

12 THE WITNESS: No, but, yeah, it's a
13 good question.

14 I mean, I think that's not the way I
15 looked at it when I wrote this.

16 I was taking all the information
17 into account: preclinical, clinical, you
18 know, information. That's how I would
19 define success, is the whole process of
20 drug development, you know, preclinical
21 and clinical and -- you know.

22

1 BY MR. CHEN:

2 Q Yeah. If a POSA -- sorry, I need to
3 say a person of ordinary skill in the art.

4 A No, that's fine.

5 Q And we're going to call it a POSA,
6 P-O-S-A.

7 A Mm-hmm.

8 Q If a POSA can make that ADC, do you
9 consider that as successful or not?

10 A Just the fact that they can
11 produce -- if a POSA can just take something
12 and produce this ADC, is that a success?

13 Q Yeah.

14 A That's what you're asking?

15 Q Yeah.

16 A Just the production of the --

17 Q The making. Yeah, the making.

18 A Making product?

19 Q Yeah, yeah.

20 A Right. Well, that's not what I had
21 in mind when I wrote this --

22 Q Okay.

1 A -- but I'll have to say that there
2 is some -- well, there is some -- a lot of
3 knowledge required to make an ADC from
4 scratch, basically. I think that's something
5 that I wouldn't -- I wouldn't judge as -- I'm
6 not sure like from a legal perspective, but
7 from a clinical perspective or something, I
8 wouldn't say that's a success.

9 It's a personal success story, I
10 would say, you know, for that person, but I
11 wouldn't say the product is successful.

12 Q No, no, that's not my question.

13 My question again -- do I need to
14 read it back to you?

15 My question is that if a POSA can
16 make an ADC, do you consider that as
17 successful or not?

18 MR. QIU: Objection, asked and
19 answered.

20 BY MR. CHEN:

21 Q Is it yes or no to the question?

22 A For this person, I think the

1 generation of just the product is not enough,
2 I think, to define it as successful.

3 Q Okay.

4 A Yeah.

5 Q Okay. So the factors include here,
6 right? There are five factors you put in
7 the -- in your declaration, right?

8 The first one is characteristics of
9 the target, whether a target antigen can be
10 internalized or not, right? And the
11 expression level of the target antigen,
12 differentials of expression level of target
13 antigen between cancer cells and normal cells,
14 and whether the target antigen has an
15 extracellular domain, or ECD, that is soluble
16 in the blood.

17 So for the first factor, right,
18 characteristic of target, that's EGFR, right?
19 So that we are talking about EGFR here.

20 A In this case.

21 Q In this case, and we don't -- I
22 think it says already the factor here.

1 We don't need to go into that details.

2 And the second factor is
3 "characteristics of monoclonal antibody,
4 specificity of the monoclonal antibody to the
5 target antigen (preferably no cross-reaction
6 with other proteins), stability of the
7 monoclonal antibody, and whether the complex
8 of the monoclonal antibody and the target can
9 be endocytosed into the cell."

10 So the endocytose, right, to the
11 cell, that's internalization, right, of ADC,
12 correct?

13 A Yeah, I think that's some form of,
14 yeah, internalization, I would guess.

15 Q So for this factor, factor 2, do you
16 believe that BA03 satisfied factor 2?

17 A So whether it gets internalized?

18 Q No, no, no. I'm looking at factor 2
19 itself, right? Factor 2.

20 A So whether it's specific --

21 Q BA03 satisfy factor 2?

22 MR. QIU: Objection, unclear.

1 BY MR. CHEN:

2 Q Yeah, let me rephrase.

3 Do you believe BA03 satisfy factor 2
4 here?

5 MR. QIU: Objection, unclear.

6 THE WITNESS: It says -- for
7 factor 2, it says it measures -- like it
8 mentions a list of things, right?

9 BY MR. CHEN:

10 Q Yeah.

11 A It's a checklist of things, right?

12 And it says -- like the subtitle is
13 characteristics of the monoclonal antibody,
14 and then it's giving you some examples.

15 Q Yeah.

16 A So what exactly are you interested
17 in? What do you mean? Like does it fulfill
18 what?

19 Q So my question is -- okay, if we
20 want to go through each subfactor, is BA03 as
21 an antibody specific enough to target EGFR
22 versus other protein?

1 MR. QIU: Objection, form.

2 THE WITNESS: Yeah. What does
3 "specific enough" mean? What do you mean
4 by "specific enough"? What does that
5 mean?

6 BY MR. CHEN:

7 Q You don't know if BA03 is a specific
8 binding to EGFR?

9 A Well, no, yeah, it's binding to
10 EGFR, but you were asking me is it specific
11 enough? What does -- what do you mean by
12 "specific enough"? I mean, what's the cutoff?
13 What does that mean?

14 Q Okay, like a tenfold binding --
15 tenfold binding affinity difference between
16 tumor cell and the normal cell -- or the other
17 product, sorry.

18 A There's something wrong with that
19 question.

20 MR. QIU: Objection, form.

21 THE WITNESS: I mean, you know, if
22 you have a tumor cell -- I mean, you know

1 what I mean.

2 BY MR. CHEN:

3 Q Yeah, yeah, yeah.

4 A I mean, if the healthy cell has
5 EGFR, they both have the same level, I mean,
6 there's not going to be a difference most
7 likely, you know.

8 BY MR. CHEN:

9 Q Fine, fine.

10 A So I don't --

11 Q So you list here, right, there's a
12 number of factors, including the specificity
13 of the monoclonal antibody and the stability
14 of monoclonal antibody, and also the
15 internalization, but have you discussed that
16 in your declaration?

17 A I discussed the specificity, yeah,
18 of the antibody. I'm saying it's an EGFR
19 specific antibody.

20 Q Okay. BA03 is one of them?

21 A Hmm? BA03, yeah.

22 Q That's my question. BA03 is one of

1 the anti-EGFR antibody, right? And you're
2 saying you discussed that specificity in your
3 declaration, but did you discuss the stability
4 of the anti-EGFR antibody in your declaration?

5 MR. QIU: Objection, form.

6 THE WITNESS: Yeah, I'm not sure I
7 discussed the stability separately from
8 everything else. I don't think there's a
9 check or anything on the stability.

10 I'm referencing, obviously, I mean,
11 Li Yu and people who've looked into this,
12 but I'm not discussing it separately --

13 BY MR. CHEN:

14 Q Okay.

15 A -- in my -- in my declaration.

16 Q But in your declaration -- sorry
17 about that.

18 In your declaration, you criticize
19 Dr. Bournazos not considering all the factors,
20 but yourself did not discuss stability of the
21 antibody in your declaration; is that right?

22 A I'm not --

1 MR. QIU: Objection, form.

2 THE WITNESS: I'm not -- I don't
3 think I'm saying I'm criticizing him for
4 not discussing all the factors.

5 I'm saying I wish he had -- they had
6 taken certain factors into account,
7 you know. So that's what I'm saying,
8 I think specifically in terms of,
9 you know, selectivity of the antibody,
10 pH dependence, and so forth.

11 But I don't think I'm saying he
12 didn't discuss all the factors and I'm
13 doing the same. I don't think that's --

14 BY MR. CHEN:

15 Q So in paragraph 82, right, again the
16 first sentence I'm reading.

17 "Designing an ADC is a sophisticated
18 process. In determining whether an ADC is
19 expected to be successful, a POSA would have
20 analyzed a series of factors," right?

21 A Mm-hmm.

22 Q You listed these factors.

1 But you just mentioned that, even
2 you list all these factors, but yourself did
3 not talk about stability of the antibody in
4 your declaration; is that right?

5 A Yes, that's correct.

6 Q Okay, let's move on to factor 3,
7 "characteristics of small molecule drug:
8 Potency of the cytotoxicity of the small
9 molecule drug, stability thereof in blood, and
10 toxicity of the in vivo metabolites of the ADC
11 containing the small molecule drug."

12 Did you discuss factor 3 at all in
13 your declaration?

14 A No. I think there are certain
15 factors that I did not address that I
16 considered of relevance, but -- and where I
17 said he did not discuss them, but I think I
18 discussed the vast -- like the majority of
19 things that are listed here.

20 I'm discussing them still. I mean,
21 I'm discussing the linker, for example, I'm
22 discussing the characteristics of the

1 monoclonal antibody --

2 Q Yeah.

3 A -- and I'm discussing the --

4 Q Did you discuss -- go ahead.

5 A -- characteristics of the target in
6 great detail.

7 Q Mm-hmm.

8 A So I think there are several
9 important points, and I could have more. You
10 know, there are several other things that --
11 I'm not saying, well, I expected him to
12 discuss everything, and I'm doing that, I'm
13 discussing all the factors. That's not what
14 I'm saying, you know.

15 Q Yeah, I'm trying to understand what
16 exactly you discuss and what you did not.

17 For example, like for potency of the
18 cytotoxicity of the small molecule drug, did
19 you discuss that in your declaration?

20 A No. All I'm saying is that these
21 are -- it is a very potent drug, but I'm not
22 going into details.

1 Q But they are a part of ADC though,
2 right?

3 A Potency?

4 Q No, the small molecule is a part of
5 ADC, right?

6 A Yeah. I mean, you know, yeah.

7 Q Right. ADC is the one -- also is
8 part of the reason why it kill tumor cell,
9 right?

10 MR. QIU: Objection, unclear.

11 THE WITNESS: ADC is part of --

12 BY MR. CHEN:

13 Q No. The small molecule is a part of
14 ADC that kill tumor cell, right?

15 A No, not necessarily. I think it can
16 be a small molecule, but it could be something
17 else as well.

18 Q What else?

19 A Yeah, chemotherapy, like a different
20 type of chemotherapy.

21 Q No, we're talking about ADC here.

22 A Yeah, I know.

1 Q Small molecule.

2 Chemotherapy is small molecule, no?

3 MR. QIU: Objection, unclear.

4 THE WITNESS: So typically, no, I
5 don't think that that's what they mean by
6 small molecule. I don't think that
7 that's what they mean.

8 It typically means something like a
9 different type of a factor molecule, like
10 tyrosine kinase inhibitor, or something
11 like that.

12 BY MR. CHEN:

13 Q But I want to ask you a simple
14 question. Did you discuss the potency of the
15 small molecule in your declaration?

16 A I'm mentioning potency, but not in a
17 very detailed manner.

18 Q Where is it?

19 A Oh, I can point you to it. I can
20 find it. I know 100% it's there.

21 Q Okay.

22 A I can find it, but it's going to

1 take me a few minutes.

2 But I'm saying there were a lot of
3 potent, for example, payloads available at the
4 time. That's where I'm discussing potency,
5 for example.

6 Q Okay. But you did not analyze that
7 in the context of safety, right, of ADC, did
8 you?

9 A I did not, you know, add specific
10 numbers in terms of potency for this and
11 discuss the numbers, if that's what you're
12 asking, you know.

13 Q Yeah. I guess my question is can
14 the characteristics of the small molecule
15 affect the safety of ADC?

16 A Yeah. I mean, that's what I'm
17 saying, that all the different components of
18 an ADC can influence its safety, every single
19 one I think.

20 Q Okay.

21 A Yeah.

22 Q Every single one, right?

1 A Every single component.

2 Q Antibody, linker --

3 A Yeah.

4 Q -- small molecule all can affect the
5 safety of ADC, right? Correct?

6 A I think all different components,
7 yes, can potentially affect the safety.

8 Q Yeah, yeah. The reason I mention
9 that is, in your paragraph 83, you probably
10 don't remember you said that, but you say
11 that, "I observe that Dr. Bournazos --

12 A Yeah, I know.

13 Q -- "does not discuss the vast
14 majority of these considerations, especially
15 with respect to the question of whether there
16 would have been a reasonable expectation of
17 success. "

18 That's why I ask you, did you
19 yourself discuss all these factors in your
20 declaration?

21 MR. QIU: Objection, asked and
22 answered.

1 THE WITNESS: Yeah, so I think I've
2 answered this three times. I did answer.

3 No, I did not address all the
4 questions said on this. I'm just listing
5 the questions that could be of
6 importance, but I did think I did address
7 the points that I found most important,
8 you know, in determining, well, the
9 success, or whatever you want to call it.
10 You just were talking about toxicity
11 yourself.

12 BY MR. CHEN:

13 Q Yeah.

14 A So I did address I think several
15 factors that are of importance where I felt
16 they did not receive enough attention -- they
17 have not received enough attention before.

18 Q So in your paragraph 84, you start
19 considering -- you're saying you're
20 "[c]onsidering the factors of 'differentials
21 of expression level of target antigen between
22 cancer cells and normal cells' and 'the

1 balance between cancer killing activity of ADC
2 and its toxicity, ' right?

3 A Yeah.

4 Q So out of all the factors you listed
5 above, you were actually only talking about
6 the differential expression level of the
7 target antigen between cancer cells and normal
8 cells and the balance between cancer killing
9 activity of ADC and its cytotoxicity, right --
10 toxicity, right?

11 MR. QIU: Objection, mis- --

12 BY MR. CHEN:

13 Q That's one part of the main factor
14 you listed.

15 A No --

16 MR. QIU: Objection.

17 THE WITNESS: -- that's not true.

18 MR. QIU: Objection,
19 mischaracterizes testimony.

20 THE WITNESS: Yeah, that's not true.

21 You know that that's not true.

22 I'm just talking about -- I mean,

1 that's one of the things, correct.

2 That's point number one.

3 But I put a lot of weight on the
4 characteristics of the antibody. I put a
5 lot of weight on the characteristics of
6 the linker. I put a lot of weight on
7 the, you know, characteristics -- yeah, I
8 guess that's the characteristics of the
9 antibody. I talk about affinity, you
10 know, but also, you know, specificity in
11 the sense of pH selectivity.

12 I talk about all these things. I
13 don't think that that's something that
14 has received a lot of attention before,
15 at least that was my impression.

16 BY MR. CHEN:

17 Q Sure, we can go back one by one what
18 you mentioned about linker, pH selectivity.

19 We want to go back one by one.

20 So I want to ask you to look at the
21 paragraph 84 again, and then towards the end
22 of paragraph 84, what you say here is --

1 that's on page 42. Page 42.

2 Are you on page 42?

3 A Yeah, yes.

4 Q Okay. Page 42, number five -- four
5 lines from the top. "A POSA would have
6 expected such a balance to be impossible for
7 the proposed BA03-vc-MMAE ADC because (1) the
8 BA03 antibody has no ability to distinguish
9 tumor and normal cells and (2) BA03's
10 higher-than-cetuximab binding affinity would
11 have caused the BA03-vc-MMAE ADC to have an
12 even narrower therapeutic window than the
13 cetuximab-vc-MMAE ADC, which was known to be
14 unviable," okay?

15 A Yes.

16 Q You understand that BA03 is
17 successful in the clinical trial, right?

18 A Yeah, I do understand that. I've
19 used this drug.

20 Q So which means your prediction is
21 incorrect, right? Your prediction here is
22 saying that the BA03-vc-MMAE, which is

1 MRG003 --

2 A Yeah.

3 Q You are saying they have narrower or
4 no therapeutic window, but the truth is MRG003
5 is very successful in the clinical trial.

6 A Yes.

7 MR. QIU: Objection, form.

8 THE WITNESS: But that's
9 something -- that's not what this
10 question was about.

11 The question was about, back then in
12 2015 -- you know, before 2014 -- would a
13 person or a POSA have thought that
14 that's, you know, something that's going
15 to be more or less successful than --
16 well, even without comparing it to
17 cetuximab, but that's what I was talking
18 about.

19 BY MR. CHEN:

20 Q Right, but your prediction was
21 wrong, though?

22 MR. QIU: Objection, asked and

1 answered.

2 THE WITNESS: Yeah, well, I mean --
3 well, you know, yeah, maybe it's wrong,
4 but I wasn't asked to find out whether,
5 you know, the opinion that the POSA had
6 back then, did it turn out to be right or
7 wrong.

8 BY MR. CHEN:

9 Q Okay.

10 A That's not what I was asked.

11 Q Let's go back to a POSA knew at the
12 time the invention was made, the first part
13 you mentioned, that BA03 antibody has no
14 ability to distinguish tumor and normal cell.

15 How did you know that?

16 A Because of the characteristics of
17 the antibody, because of the characteristics
18 of the antibody. Like, you know --

19 Q Such as?

20 A Yeah, I could give -- I mean, I
21 have -- if you want to look at my beautiful
22 table that has all the factors in that that

1 you can use to improve a person's -- an
2 antibody's selectivity --

3 Q Which reference --

4 A -- we can go over that.

5 Q Which reference disclosing BA03?

6 A So that's --

7 MR. QIU: Objection, form.

8 BY MR. CHEN:

9 Q Which reference disclose BA03?

10 A So you just asked me a different
11 question?

12 Q No, I'm asking you a simple
13 question. Your knowledge about BA03 come from
14 where?

15 A It comes from different sources, and
16 one of them would be the Liu reference.

17 Q Liu reference, right.

18 Give me a copy of Liu reference.

19 Let me ask you, does Liu reference
20 tell you BA03 antibody has no ability to
21 distinguish tumor or normal cell?

22 MR. QIU: Objection, form.

1 MR. CHOI: What's the exhibit
2 number?

3 MR. CHEN: 108 -- 1008.

4 THE WITNESS: I'm not even sure I
5 need to look at this because I don't
6 think that that's --

7 BY MR. CHEN:

8 Q You don't think that --

9 A No one would say that. I mean, this
10 is not something that you don't know.

11 Q So Liu reference --

12 A That's my opinion, like summarizing,
13 you know, the findings, but I don't think --
14 I'm not saying that Liu said there's no --
15 that this antibody is not able to distinguish.
16 I'm not saying that.

17 Q Right. So when you have an opinion,
18 we're going to ask you what factual basis you
19 rely on --

20 A Yeah, that's fine.

21 Q -- because you can't just come up
22 with a conclusion by itself without relying on

1 the knowledge in the references.

2 For example, if Liu is the only
3 reference disclose BA03, I want you to tell me
4 where in Liu it actually say, Liu, BA03
5 antibody cannot -- has no ability to
6 distinguish tumor and normal cells.

7 MR. QIU: Objection, form.

8 Objection, argumentative.

9 BY MR. CHEN:

10 Q So you're saying you couldn't find
11 that. You don't think you disclosed that,
12 right?

13 A Well, yeah, I don't think that
14 that's what -- I mean, you know, I don't think
15 that that's what I said, that that's what I'm
16 saying in my declaration, and I don't think --
17 no, I don't think I'm saying, Liu is saying --

18 Q Right.

19 A -- it's not able to distinguish
20 between, but based on the characteristics that
21 I'm showing in my table, and I have the
22 references right next to them, no, that's -- I

1 mean, that's the easiest way to go over all
2 this.

3 Q I'm asking you the direct reference
4 that really disclose BA03 is the Liu
5 reference. I'm asking you, did Liu disclose
6 that BA03 antibody has no ability to
7 distinguish tumor and normal cells? You say
8 no, right?

9 A Yeah, I think that --

10 MR. QIU: Objection, asked and
11 answered.

12 THE WITNESS: I've answered this
13 several times.

14 BY MR. CHEN:

15 Q That's good. Let's move on to the
16 second statement you say, "BA03's
17 higher-than-cetuximab binding affinity would
18 have caused the BA03-vc-MMAE ADC to have an
19 even narrower therapeutic window than the
20 cetuximab-vc-MMAE ADC."

21 So let me just focus on the first
22 part of the sentence, "BA03's

1 higher-than-cetuximab binding affinity."

2 Where did you -- where did you know that? How
3 did you know that?

4 A That the BA03 has a higher
5 affinity --

6 Q Than cetuximab. How did you know
7 that?

8 A -- than cetuximab?

9 I think that was -- let me see.

10 Q So, Doctor, you actually mentioned
11 that in paragraph 61.

12 MR. QIU: Counsel, there's a
13 question pending. Do you want the
14 witness to answer that question?

15 MR. CHEN: Sure. I was just trying
16 to help him.

17 MR. QIU: Okay, or you can maybe say
18 what you want to say and maybe renew the
19 question.

20 MR. CHEN: Okay.

21 BY MR. CHEN:

22 Q So, Doctor, so we were on -- let me

1 see. We were on the previous paragraph. I
2 tried to -- okay. We were on paragraph 84,
3 right? So as counsel requested, I'm going to
4 repeat my question.

5 In your -- in your statement, you
6 say that "BA03's higher-than-cetuximab binding
7 affinity." So my question is how do you know
8 that? How do you know BA03 has a higher
9 affinity than cetuximab? Based on what?

10 A Let me check quickly.

11 So what I'm saying is -- I'm talking
12 about this whole thing in number 3.

13 Q Number 3?

14 A So that's 60, paragraph 60 and 61.

15 Q Yeah.

16 A So that's where I'm explaining what
17 you just said. I mean, you just said -- like
18 we were just talking about, you know, the
19 summary that I'm providing under 82 and so
20 forth, and what I'm saying is that, "As
21 disclosed in Liu and stressed by
22 Dr. Bournazos, the BA03 antibody has a higher

1 binding affinity --

2 BY MR. CHEN:

3 Q Paragraph 61 is what you're reading?
4 Paragraph 61?

5 A Yes.

6 Q So you are -- you cite what, like
7 Exhibit 1008, paragraph 140; is that right?

8 A Yes.

9 Q Okay, let's take a look. Do I have
10 Liu? Do you have Liu? Okay. Counsel?

11 MR. QIU: Thank you.

12 BY MR. CHEN:

13 Q So let's go to paragraph 140 then.
14 So are you on paragraph 140?

15 A Yes.

16 Q Can you tell me where they're
17 talking about binding affinity there in 140?

18 A So in 140 they're talking about
19 binding affinity?

20 Q No, I'm asking you. So you are
21 citing paragraph 140 for your support about
22 the BA03 has a higher binding affinity than

1 cetuximab.

2 A Yes.

3 Q Can you tell me where exactly
4 paragraph 140 is talking about the binding
5 affinity?

6 A Let me see. So they're performing
7 this as a -- well, it's in there.

8 Do you want me to read it to you?

9 Q You know why I'm asking, right?
10 It's not in there.

11 Let me ask you, where is it?

12 A Well, "The results indicate that the
13 humanized antibodies BA03 ... of the present
14 invention have higher binding activity than
15 Erbixux ... while BB03 and BC03 are similar to
16 Erbixux."

17 Q Which sentence?

18 A Here.

19 Q Line?

20 A Well, I don't know what line it is,
21 I'm sorry, but that's on page 15, second
22 paragraph, 140.

1 Q Yeah.

2 A So they're saying that's the readout
3 is the EC50.

4 Q Yeah, the EC50, right?

5 A Was calculated using this and that
6 software, and results are shown in Table 2.
7 "The results indicate that the humanized
8 antibodies BA03 and BD03 of the present
9 invention have higher binding activity than
10 Erbitux ... are similar to Erbitux."

11 I don't know what the question is.

12 Q So which one is BA03?

13 A BA03 is mentioned, right, so that's
14 in the table.

15 Q Okay, BA03 has higher binding. So
16 this is a major part, EC50, right?

17 A Yes.

18 Q Is that right?

19 A Yes.

20 Q Is another direct assay to major --
21 EC50 is a different concept of defining
22 affinity, right?

1 A No, no.

2 Q Are you sure?

3 A Yes, I'm sure, yeah.

4 Q EC50 is measuring the activity,
5 correct?

6 A No -- yeah, it's measuring the
7 dissociation rate of the -- of the -- of the
8 receptor like, you know, and it has the -- I
9 don't know what the problem -- I mean, it has
10 everything in there. It even has the
11 nimotuzumab in there.

12 Q Yeah, I know that.

13 A Everything, so what's the problem?

14 Q I'm asking you the concept between
15 EC50 and binding affinity, because EC50, is
16 that -- EC50 here is measured based on the
17 cell assay, cell-based assay, right? It's
18 based off the --

19 A Yeah.

20 Q If you're reading paragraph 140
21 here, it's A forty --

22 A Yeah, A431.

1 Q It's a cell-based assay, right?

2 A Yes, yeah.

3 Q It's measuring activity, right?

4 A Hmm?

5 Q It's measuring activity of the
6 antibody?

7 MR. QIU: Objection --

8 THE WITNESS: Yeah.

9 MR. QIU: -- asked and answered.

10 THE WITNESS: I mean, that's -- the
11 activity of the antibody is like --
12 that's a function of its affinity.

13 I mean, I don't know what the -- I
14 don't know what your problem is with
15 this.

16 BY MR. CHEN:

17 Q Well, my problem is I don't -- I
18 need to understand. Affinity is not
19 necessarily equivalent with activity.
20 Affinity is not a concept as activity.

21 A I think --

22 MR. QIU: Objection, form.

1 BY MR. CHEN:

2 Q Correct?

3 A No, I don't -- I couldn't -- I can't
4 subscribe to that.

5 Q You say that affinity is the same
6 function --

7 A I think that's one expression, yeah,
8 that you can use to measure affinity, and
9 I think that's what they did.

10 Q Okay, you think best.

11 Can you go back to your declaration,
12 paragraph 65, please.

13 Okay, paragraph 65, and actually go
14 to page 34, there's a sentence right above
15 paragraph 66, okay?

16 A So page 34.

17 Q Next page, okay. So the sentence
18 right above paragraph 66, I want to read that
19 to you.

20 "The BA03 antibody, by contrast,
21 does not have tumor-targeting pH-selectivity,
22 much less at an enhanced level that is

1 comparable to huY104D. "

2 How did you know BA03 doesn't have
3 pH selectivity?

4 A Well, I think one is -- one thing
5 that I'm obviously using is the -- is the Wei
6 publication that has the human on non-human
7 Y104D, right?

8 Q Yeah.

9 A I mean, that's what it's describing,
10 right, is the 104D.

11 Q Can I ask you, so are you saying
12 that as long as antibody doesn't have Y104D
13 mutation, then it doesn't have pH selectivity?
14 That's your logic?

15 MR. QIU: Objection,
16 mischaracterizes testimony.

17 THE WITNESS: No.

18 BY MR. CHEN:

19 Q No?

20 A That's not what I was saying.

21 Q Yeah, go ahead. Yeah, how do you
22 know the BA03 doesn't have pH selectivity?

1 MR. QIU: Objection, asked and
2 answered.

3 MR. CHEN: He hasn't answered yet.

4 THE WITNESS: So I can find out like
5 what exactly.

6 BY MR. CHEN:

7 Q That's okay, take your time. If you
8 can find it in your declaration, find it.

9 A Yeah, no, yeah, I'm looking at it
10 right now, but I'm not even looking for it
11 because I'm just trying to remember.

12 I think the way I looked at it is,
13 so first of all, Wei is showing that their
14 antibody, the 104D, in its human form, for
15 example, has pH selectivity. That's what they
16 are showing, right, over cetuximab.

17 And my main conclusion was that,
18 you know, BA03 is -- is a --

19 Q No, go ahead.

20 A You know, so is a derivant of
21 cetuximab, that where no changes were
22 performed that could have resulted in

1 pH selectivity.

2 So I think, if I'm correct, but I
3 could be wrong, but I'm willing to check,
4 that's primarily how I -- so I derived the
5 non-existent pH selectivity from the one from
6 cetuximab because I think that's pretty close
7 in terms of, you know, the design of the
8 antibody parts that matter to pH selectivity.

9 And then I was looking at the
10 results from Wei. I think there was something
11 else also. Let me just check very quickly.
12 There was more than that even.

13 Q Feel free to take your time to look
14 at your declaration. You do have a portion in
15 your declaration discussing the pH
16 selectivity.

17 I want to understand what's the
18 scientific basis that you draw that conclusion
19 that BA03 doesn't have pH selectivity.

20 A So the one thing is -- so I'm
21 talking about detail in all this -- about all
22 this. And that's not all, but I would

1 say it's --

2 Q Which paragraph?

3 A This is 56, 57, and 58.

4 Q Okay.

5 A And, well, I can read this whole

6 thing, but it really --

7 Q No, no. If you don't mind, will you
8 explain to me?

9 A It addresses everything.

10 Q So 56, right?

11 A So 56 explains how this is typically
12 done, and what we are saying is basically
13 that's not what was done for the BA03
14 antibody. So that's number one.

15 Q Hold on just a second, let me ask
16 you. So Wei to gain pH selectivity, how many
17 mutations that Wei made?

18 A Oh, they did -- I think they only
19 did one mutation. They exchanged just one
20 amino acid, if I'm correct, out of 104, the
21 YD.

22 Q They make many, right?

1 A Oh, they made different variants.

2 Q They screen for that, right?

3 A Oh, yeah, they have a whole list of
4 the things, you know.

5 Q They identify Y104P, right?

6 A They did.

7 Q Single mutation, right?

8 A Yeah.

9 Q Only one residue changed, right?

10 A I think so, if I remember correctly,
11 you know.

12 Q How many mutations BA03 versus
13 cetuximab?

14 A Yeah.

15 MR. QIU: Objection, form.

16 BY MR. CHEN:

17 Q Do you know?

18 A Well, I would have to go back, but I
19 don't think it's -- I think -- I don't think
20 it's of relevance, the number of mutation. As
21 long as they're in a different region, I don't
22 think that that's something that matters.

1 Q So your rationale is that in order
2 to have a pH selectivity, you have to make
3 mutation on 104; is that right?

4 A No, no, no, no, no.

5 MR. QIU: Objection,
6 mischaracterizes testimony.

7 THE REPORTER: Wait, everyone is
8 talking over each other, please.

9 BY MR. CHEN:

10 Q It's a question. I didn't mean to
11 mischaracterize asking is it Wei or not.

12 What's your scientific basis to
13 predict BA03 does not have pH selectivity?
14 Based on what? Based on the sequence
15 differences, or based on what?

16 MR. QIU: Objection, form.

17 THE WITNESS: It's based on a
18 variety of things. It's not just one.

19 BY MR. CHEN:

20 Q Such as?

21 A You know, yeah, I was just starting.

22 One is 56. You know, so that's the

1 mutation where it talks about mutation in the
2 CDR that can potentially use -- lead to --
3 lead to pH sensitivity.

4 I'd have to add to this, and it's
5 also, if you look at Wei in detail, which I
6 have, I mean, you'll find out that it's not
7 easy. Like you can introduce a whole variety
8 of mutations, and it's not easy to get a clone
9 that will be pH selective.

10 I can tell you that because I've
11 done it myself, and it's very, very hard to
12 come up with a -- with a -- with a clone
13 that's -- that's pH selective. So I think --
14 so they didn't do what Wei did, so that's one
15 thing. So number two --

16 Q Can I just --

17 MR. QIU: Counsel, let the witness
18 finish.

19 BY MR. CHEN:

20 Q Yeah, go ahead.

21 A So then I think, for some reason,
22 the question came up with a humanization. I

1 don't know why, but that came up during a
2 previous proceeding, something whether
3 humanization alone can lead to pH sensitivity
4 or be related to a pH sensitivity, and I think
5 that came up before I came on board.

6 So then I'm answering, no, that
7 factor does also not explain, or at least
8 suggest pH selectivity, because they're
9 unrelated more or less, you know, humanization
10 and pH selectivity.

11 So then I'm saying -- I'm citing
12 Petitioner's own experiments that also
13 confirmed that BA03 does not have pH
14 selectivity, and I'm citing with '382
15 application as a reference as well.

16 BY MR. CHEN:

17 Q Okay.

18 A I mean, and there are more and more.
19 It's just, you know, I could -- it's just --

20 Q So the paragraph 58, right, you
21 mentioned '382 application, right?

22 A Mm-hmm.

1 Q When was that application published?

2 A Oh, my gosh, I mean, that's
3 something that I don't know off the bat.

4 Q When was that filed?

5 A I saw it was filed in November of
6 '22.

7 Q So the filing -- so this reference
8 has to be published like after that filing
9 date, right? 2022, it has to be filed --

10 A It was published outside, yes.

11 Q After 2022, right?

12 A Yes, right.

13 Q So a POSA wouldn't be able to know
14 at the time of the filing date of the
15 challenged patent about this -- what you
16 discuss in paragraph 58, right? A POSA
17 wouldn't be able to know that, right?

18 A That's a part that they probably
19 wouldn't have known, yeah. That's something
20 that we know now, right, yeah.

21 Q Doesn't matter, right? We're
22 talking about a POSA would know it from --

1 MR. QIU: Objection, form.

2 THE WITNESS: It doesn't -- I'm not
3 saying it doesn't matter. I mean, we had
4 this same argument before.

5 BY MR. CHEN:

6 Q Yeah.

7 A I'm just saying it did not allow
8 anyone to predict something back then, but it
9 matters because it confirms what we
10 predicted -- what I would have predicted back
11 then retrospectively confirms that that's
12 actually the case, you know.

13 Q If you said you can use that
14 information, I do not say the result from the
15 clinical trial MRG003 can work, your
16 prediction is entirely wrong. Can I use that
17 information, like post-filing results?

18 A Well --

19 MR. QIU: Objection, calls for legal
20 opinion.

21 THE WITNESS: No, I'm not -- sorry,
22 sorry.

1 I'm not asking -- that's the thing.

2 I'm not looking at this from a legal
3 perspective. I'm looking at this like --
4 as you did previously with the other
5 example.

6 I'm saying, well, yes, it can. It
7 means something, right, it proves
8 something, but you couldn't have used
9 this to predict anything.

10 That's what I just said.

11 BY MR. CHEN:

12 Q So if we cannot use that to predict,
13 then really your reasonings rely on
14 paragraph 56 and 57, so let's talk about
15 paragraph 56 and paragraph 57 then.

16 So what exactly you try to say in
17 paragraph 57?

18 MR. QIU: Objection, unclear.

19 BY MR. CHEN:

20 Q I can rephrase that if you want me
21 to, but I try to understand what do you mean
22 in paragraph 57 of your declaration?

1 MR. QIU: Objection, unclear.

2 THE WITNESS: Yeah, if you could
3 just define a little more, like what your
4 question is in terms of this.

5 BY MR. CHEN:

6 Q Can you explain paragraph 57?
7 That's your own statement.

8 A Yes.

9 Q Yeah, explain to me what you really
10 want to say here. I try not to put words in
11 your mouth, but I try to ask you to explain
12 your -- what you say here.

13 A What I am saying is -- so this whole
14 paragraph is about the relation of
15 humanization of an antibody with pH
16 selectivity. That's what this is about, so
17 this is what this is supposed to address.

18 Q Are you saying that humanization
19 doesn't matter, does not affect pH
20 selectivity? That's what you say?

21 A No, what I'm saying -- that's not
22 what I'm saying. I'm not saying -- I never --

1 I don't think I put a lot of general
2 statements in there, but I'm saying it does
3 not necessarily predict pH selectivity. Most
4 of the times it won't, actually, I think.

5 And then I'm explaining why that is,
6 like although I don't think that's even
7 necessary, because we have so many examples
8 out there of humanized antibody, or even human
9 antibodies, and only like a tiny minority of
10 these antibodies have pH selectivity. It's
11 just so -- I mean, I can give you one of our
12 publications.

13 It's just so unlikely for anything
14 to really cause pH selectivity unless you
15 target pH selectivity specifically, or you try
16 a huge array of mutations, and then select.

17 So I'm just saying, so the selective
18 mutations that you induce in the framework
19 regions to humanize an antibody, first of all,
20 I mean, they typically avoid, obviously,
21 interfering with the binding characteristics
22 of the antibody.

1 Q Such as how? How do they avoid
2 that?

3 A Well, you try to avoid regions that
4 are, you know, dominant in defining binding of
5 the antibody to its target.

6 Q The CDR?

7 A Well, in the variable regions, like
8 any, you know, amino acid.

9 I mean, I can't go, I mean, into
10 details with that, but there are residues that
11 we know from antibodies that are dominant in
12 defining the binding of an antibody, and
13 you're obviously trying to avoid these regions
14 when you try to humanize an antibody because
15 you don't want to interfere with the
16 antibody's affinity or binding in general.

17 So -- and I think, you know, first
18 of all, I'm saying, in this specific context,
19 there's no reason really to believe that
20 humanization led to any change in pH
21 selectivity. It's just extremely unlikely.
22 You know, it's extremely unlikely.

1 And the other thing is, for any
2 antibody, even if it's not about specifically
3 about humanization, but about, you know, just
4 inducing random mutations, for example, even
5 then it's extremely unlikely that your result
6 will be an antibody that has a significantly
7 different pH selectivity.

8 Q Wei is also doing screening, right?

9 A Yeah.

10 Q Wei did the random mutagenesis, and
11 then select one antibody to proceed with
12 additional study, right?

13 A Mm-hmm.

14 Q And why did you say that even random
15 mutagenesis, you cannot identify pH
16 selectivity variant?

17 MR. QIU: Objection,
18 mischaracterizes testimony.

19 THE WITNESS: Yeah, so that's not
20 what I -- so I just recognized -- I just
21 recognized what you are saying --

22

1 BY MR. CHEN:

2 Q Yeah.

3 A -- by saying that's what they did.

4 All I'm saying is it's not easy.

5 It's a very, very difficult process, and to
6 just, well, randomly arrive at an antibody
7 with increased pH selectivity, in my opinion,
8 is almost impossible, you know.

9 Q So are you aware that BA03 also had
10 mutation in the CDR region?

11 A Yes.

12 Q Not just humanization, right?

13 A Yes.

14 Q Does that also have additional
15 mutation in CDR region?

16 A Yes, yeah.

17 Q Then how do you be certain that will
18 not give pH selectivity property to BA03?

19 A So one is -- one would be, I mean,
20 the experiments that we just looked at, right,
21 in the Petitioner's document.

22 Q What was that? I don't know. What

1 experiment are you talking about?

2 A Oh, sorry. Oh, God, I'm confused
3 now. Well, no.

4 Q Scientifically, yeah.

5 A No, that's what we -- yeah, we
6 looked at the '382 application, right, and
7 its -- and its --

8 Q '382 application was not available
9 to a POSA at the time that --

10 A Yeah, right. Yeah, right. No, no,
11 yeah, yeah. No, I'm just -- I'm just
12 recapitulating what was said before.

13 So if we're only looking at things
14 that were available before --

15 Q Yeah.

16 A -- I would say the same thing that I
17 just said. I think just, you know, random --
18 a mutation, especially if they were introduced
19 to change other characteristics of the
20 antibody, I think it's like extremely unlikely
21 that at the same time they will cause pH
22 selectivity.

1 It's almost -- I mean, I think -- I
2 would say it's unheard of, but, you know,
3 I think it's extremely unlikely.

4 Q Wei went through the same process
5 when the mutagenesis identify a number of
6 variants actually have pH selectivity, and now
7 you are saying that you cannot -- it's very
8 unlikely to identify a pH-selectivity variant.
9 I don't understand that.

10 MR. QIU: Objection, form.

11 THE WITNESS: Well, it's actually --
12 I mean, I think I've answered all these
13 before, but I can go over it again.

14 I think if your goal is to change
15 the pH selectivity, I think that was
16 Wei's -- one of their main goals was to
17 change pH selectivity.

18 So they performed these random
19 mutations, like a large number of random
20 mutations, with a goal of identifying pH
21 selective clones.

22

1 BY MR. CHEN:

2 Q Yeah.

3 A And by investing a lot of time and
4 effort into all this, they were able to find
5 clones which where I would have to say, yes,
6 there was actually some degree of pH
7 selectivity.

8 But if your goal is not to do that
9 even, and I don't think anyone has ever
10 described that as a goal for BA03 to --
11 you know, to transform the antibody into --
12 equip it with pH selectivity, I think, again,
13 I'd have to say it's -- the goal was
14 different, and I think that's why the outcome
15 is most likely very different as well, so ...

16 Q So let me ask you a question.

17 A Yeah.

18 Q So if you want to know whether or
19 not BA03 has a pH selectivity for sure, you
20 just need to do the assay, right? Do the
21 testing, right? You do the test, right?

22 A Well, yeah, I guess so.

1 Q Right? If you don't -- if you
2 didn't -- if you don't do the test, you really
3 don't know for sure that BA03 does or does not
4 have pH selectivity, right?

5 MR. QIU: Objection, calls for
6 speculation.

7 THE WITNESS: Yeah.

8 BY MR. CHEN:

9 Q You need to do testing to know for
10 sure BA03 has pH selectivity or not?

11 A If you -- well, again, it's true
12 this is like just pure speculation now. If
13 you need to know -- well, if that's the
14 case -- if you need to know with 100%
15 certainty that there is no pH selectivity, I
16 don't see why that was -- that would happen.

17 Why would someone invest a lot of
18 time and effort into like making sure that
19 there's no pH selectivity? I don't know how
20 that could -- why that would happen and how,
21 but if that were the case, then maybe -- I
22 would say yes, you would have to do the assay

1 to be sure.

2 Q Mm-hmm.

3 A But I just don't understand what the
4 relevance -- I really don't understand what
5 the relevance is, like for this situation.

6 Q Because you opined that BA03 does
7 not have pH selectivity. I try to find out --
8 I have lots of struggle understanding what you
9 say here because I --

10 A I was trying to explain that it's
11 like -- I think I would ask for actually the
12 opposite. If someone came to me and said,
13 well, my friend, BA03, maybe it has pH
14 selectivity. I'd say, well, that's something
15 that you need to prove because it's so
16 unlikely that that's the case. I seriously
17 doubt it, you know, and so that's what I
18 would do. That's my opinion.

19 Q Only if somebody want to do a --
20 make an ADC which is pH selective, right?
21 Only if they want to do that, and then they're
22 thinking, okay, is BA03 actually pH selective,

1 right?

2 MR. QIU: Objection, form.

3 BY MR. CHEN:

4 Q Only if they want to make an ADC
5 that's pH selective, right?

6 MR. QIU: Objection, form.

7 BY MR. CHEN:

8 Q Based on your logic. Otherwise, why
9 would they --

10 A Based on my logic?

11 MR. QIU: Objection, form.

12 THE REPORTER: You guys are cutting
13 each other off a lot.

14 THE WITNESS: I'm sorry. I'm sorry.
15 I think that's just too speculative.

16 You know, I would say, well, in that
17 case, why not use Wei's antibody, you
18 know, but I'm not sure. I don't know.

19 MR. QIU: Counsel, it has been going
20 for like 18 minutes about, so when you
21 have a good break point, let's take a
22 break.

1 BY MR. CHEN:

2 Q One more question related to this
3 topic.

4 Did you -- did you do a sequence
5 alignment between BA03 and cetuximab?

6 A Did I do like myself? Did I compare
7 the sequences?

8 Q Yeah, yeah.

9 A I didn't do it personally. No, I
10 did not do a sequence alignment.

11 Q Do you know what the mutation that
12 BA03 has in the variable region relative to
13 cetuximab?

14 A Right off the bat, I don't know. I
15 don't know that, no. I would have to look it
16 up.

17 Q Okay. So you don't know?

18 A No.

19 Q Okay.

20 A No, I don't know.

21 Q So you did not do sequence alignment
22 between -- or sequence comparison between BA03

1 and cetuximab, correct?

2 MR. QIU: Objection, asked and
3 answered.

4 THE WITNESS: Yeah.

5 BY MR. CHEN:

6 Q You did not?

7 A Well, I did not compare both
8 sequences, no.

9 Q Do you know anyone else did that?
10 If counsel did that?

11 MR. QIU: Objection, calls for
12 privileged information.

13 Doctor, I caution you to not reveal
14 any communication with counsel in this
15 answer.

16 BY MR. CHEN:

17 Q Let me put it differently. I don't
18 want to know your privileged information.
19 I'll put it a different way.

20 Did anyone on the team provide a
21 sequence alignment to you between BA03 versus
22 cetuximab?

1 MR. QIU: Sorry, I have to voice the
2 same objection. Objection, calls for
3 privileged information.

4 Please avoid talking about
5 communications between counsel and you.

6 BY MR. CHEN:

7 Q It's a yes or no. I don't want to
8 know exactly like what -- the content between
9 your communication with your counsel, but its
10 effects.

11 Yes or no, did you receive that --
12 any -- this kind of sequence alignment from
13 anyone in the team?

14 MR. QIU: Counsel, I think for this
15 one I would just have to instruct the
16 witness not to answer since I believe
17 there's no way to answer this question
18 without revealing privileged information.

19 BY MR. CHEN:

20 Q So, okay. Have you reviewed -- if
21 you haven't done that sequence comparison by
22 yourself, have you reviewed sequence

1 comparison between BA03 and cetuximab?

2 A Well, all I can say is I've looked
3 at sequences for different antibodies. I've
4 looked at them.

5 Q Yeah, that's not my question.

6 A I don't remember whether I like
7 compared them side by side.

8 Q Okay, you did not.

9 Okay, take a break. 10 minutes?
10 Come back at 2:15, please.

11 MR. QIU: 2:15, okay.

12 THE VIDEOGRAPHER: The time is
13 2:06 p.m. We're now off the record.

14 (A break was taken.)

15 THE VIDEOGRAPHER: The time is
16 2:14 p.m. We are now on the record.

17 BY MR. CHEN:

18 Q All right, Doctor, we are back.

19 A Good.

20 Q So I want to apologize, I'm going to
21 keep asking you this question. Let's go back
22 to paragraph 56. Sorry I have so much trouble

1 understanding what you say here, right.

2 So paragraph 56, you say,
3 "pH-selective antibodies are typically
4 obtained by substituting an amino acid residue
5 at an antigen-binding site ... in the CDRs,
6 with a histidine residue or ... [a]
7 negatively-charged [residue], aspartic acid or
8 glutamic acid," right?

9 That's what you say, right?

10 A Mm-hmm.

11 Q Okay. So let's go to Liu reference,
12 Exhibit 1008. Do you have a copy of
13 Exhibit 1008?

14 A I think it's this one.

15 Q Do you see that? So I want you to
16 take a look at the lower part of this page.
17 That's page 11. Sorry, page 11.

18 Page 11, do you see that?

19 A Yeah.

20 Q So I want to read that sentence to
21 you, okay? "The 33rd position glycine in CDR1
22 was optimized to amino acid aspartic," right?

1 "[A]nd the 100th position [threonine] in CDR3
2 was optimized to amino acid Asp," aspartic
3 acid, right?

4 A Yes.

5 Q Okay. So based on your own
6 definition, own characterization here in
7 paragraph 53 -- 56, you're saying that usually
8 to gain pH selectivity, you mutate a residue
9 to charge a residue with aspartic?

10 A Yes.

11 Q And BA03 also did that, right?

12 A Yeah, I think so, yeah.

13 Q So why don't you think BA03 doesn't
14 have pH selectivity? Based on what?

15 A Well, I think I've said all of
16 the -- I mean, I've said everything, but I can
17 repeat the same thing again.

18 I mean, that goal -- that goal was
19 to -- that's what they're saying -- was to
20 increase the affinity, increase the affinity
21 by, you know, basically modifying the
22 sequence. I think they achieved that goal by

1 doing that.

2 I think -- I still think that
3 it's -- well, I'll have to say, nothing has
4 changed. I think it's extremely unlikely that
5 the same mutation that led to the -- like an
6 increased affinity led to pH selectivity at
7 the same time.

8 Q You don't know that, right?

9 A Well, yeah, I don't know that
10 personally, you know, but I think it's -- any
11 person who knows about this at the time, they
12 would have said it's impossible, it's close to
13 impossible, it's not going to happen.

14 Q Based on what?

15 A Based on experience and published
16 literature, you know, the finding. There's
17 nothing new really. I mean, people do work on
18 pH selectivity, so ...

19 And if you -- well, I don't want to
20 go into more detail, but if you look at Wei's
21 paper, and if you read it, you can get a sense
22 for how difficult something like this is,

1 because they were really struggling to find a
2 clone that's truly pH selective. So I think
3 it's -- it's just that -- it' just --

4 Q So the question is not about how
5 much effort you need to put into in order to
6 identify a pH-selectivity variant.

7 The question is how do you know BA03
8 does not have pH selectivity even it meets
9 your requirements stated in paragraph 56?

10 You are saying that usually,
11 generally in order to obtain the pH
12 selectivity, you need to mutate a residue in
13 the CDR region with a charged residue ASP,
14 such as.

15 A Yeah, that's an example --

16 MR. QIU: Objection. Objection,
17 mischaracterizes testimony. Objection,
18 form.

19 THE WITNESS: And I've said this a
20 lot of times before.

21 Yeah, this is an example of what
22 people can do. It's just not that easy.

1 I mean, you can't just -- I mean, this is
2 not a recipe, what I'm saying, for pH --
3 generating pH-selective clones. That's
4 all I can say. That's now how it is.
5 It's not that easy, you know. This is
6 just an example.

7 And they're doing something that's
8 similar, but I think the likelihood that
9 that led to a comparable result is almost
10 zero. It's extremely low, unlikely. And
11 I think that's something that matters,
12 you know.

13 BY MR. CHEN:

14 Q But you -- again, it's not about
15 difficulty. I'm asking with BA03, how do you
16 know?

17 A No, but it's about likelihood.

18 MR. QIU: Objection, asked and
19 answered.

20 THE WITNESS: It's about likelihood,
21 I think.

22

1 BY MR. CHEN:

2 Q Likelihood, right?

3 A Yeah.

4 Q But you don't know one way or the
5 other BA03 --

6 A So --

7 MR. QIU: Objection.

8 THE REPORTER: Wait, wait --

9 BY MR. CHEN:

10 Q -- BA03 -- let me finish -- BA03
11 meet your requirement to have a mutation in
12 the CDR region?

13 A No, that's not the only requirement.
14 That's not the only requirement. That's just
15 an example.

16 I mean, I cannot say. I mean, that
17 would be -- that would be -- I mean, this is
18 not the only requirement.

19 I'm not saying, each time you do
20 introduce such a mutation, you'll get a
21 pH-selective clone. That's obviously not what
22 I'm saying.

1 Q Yeah, but my question really is how
2 do you know BA03 doesn't have pH selectivity?
3 You say you explain many times, but I still
4 don't understand. How do you know BA03
5 doesn't have pH selectivity other than it's
6 difficult?

7 MR. QIU: Objection, asked and
8 answered.

9 THE WITNESS: I think it's close to
10 impossible, that's how I know. It's just
11 the likelihood is so low.

12 I mean, anything is possible in this
13 universe, but I think you'll have to go
14 by your experience and the information
15 that's available, and all I can say --
16 and I've said this many times before --
17 I think it's just close to impossible,
18 you know. So it's as close to knowing
19 for a fact as you can get without doing
20 the experiment.

21 BY MR. CHEN:

22 Q But Wei did it, right? Wei did find

1 a number of variants have pH selectivity?

2 A Oh, people can do it. Yeah, that's
3 not what I'm saying. You can do it. That's
4 not what I've said. It's possible.

5 Q All that matter in the prior art is
6 somebody does that.

7 And can I have the Wei reference,
8 please? 1005.

9 So in your paragraph 57 of your
10 declaration, it says that BA03 -- let me know
11 you are there -- "BA03 antibody is a humanized
12 version of cetuximab," right?

13 A Yes.

14 Q "In a humanization process, many of
15 the residues in the framework regions of
16 animal origin are replaced with human
17 counterparts," right?

18 A Mm-hmm.

19 Q And, "Typically, few changes are
20 made to the CDR regions to avoid interfering
21 with the parental antibody's binding activity.
22 Therefore, unless specifically designed or

1 screened for, a typical humanization process
2 like that employed in Liu would not have
3 conveyed tumor-targeting pH-selectivity,"
4 okay?

5 So for the humanization of the BA03
6 antibody, did you look at the sequence of the
7 BA03 with respect to the changes in the
8 framework regions? Did you personally look at
9 that?

10 A I don't remember. I don't remember
11 that detail.

12 Q You did not, right?

13 A No.

14 Q So try to understand. Humanization,
15 the change is not only to Fc region, right,
16 also changes to the framework region?

17 A Mm-hmm.

18 Q And for the BA03 is a humanized
19 version of cetuximab, it also has additional
20 mutation in the CDR region, correct?

21 A It has. Yes, it does.

22 Q Okay. I think it does. Yeah, we

1 established that.

2 And then I'll give you a copy of the
3 Wei reference. Counsel?

4 MR. QIU: Thank you.

5 MR. CHEN: Can you point me to
6 the -- which one? Give me one second,
7 I'll try to refresh my memory.

8 (Mr. Chen and Mr. Choi conferring.)

9 MR. QIU: Doctor, before you answer,
10 just give me an opportunity to voice any
11 objections. Thanks.

12 BY MR. CHEN:

13 Q Put aside Wei for one moment. I
14 will come back to Wei later on.

15 Okay, next topic. So let's go to
16 your declaration, page 114.

17 So, Doctor, in your declaration, you
18 talk about -- use a word like "discouraged" a
19 lot, right? And sometimes you use "teach
20 away." I think that I can point to
21 paragraph forty -- let me read it to you.
22 Paragraph 41.

1 In paragraph 41 of your declaration,
2 you mention that, you know, "Tikhomirov's ADC
3 that has a cleavable linker, especially given
4 that Tikhomirov teaches away from such a
5 modification," right?

6 So I want to understand specifically
7 your understanding of the standard "teaching
8 away," right?

9 And then in your declaration, in
10 Appendix 3, which is on page 114, I believe
11 you're putting like your understanding of
12 "teaching away." I can read it here.

13 "I understand that obviousness may
14 be defeated if the prior art indicates that
15 the invention would not have worked for its
16 intended purpose or otherwise teaches away
17 from the invention. A reference teaches away
18 when a person of ordinary skill, upon reading
19 the reference, would be discouraged from
20 following the path set out in the reference,
21 or would be led in a direction divergent from
22 the path that was taken in the claim. A

1 reference that merely expresses a general
2 preference for an alternative invention but
3 does not criticize, discredit, or otherwise
4 discourage investigation into the claimed
5 invention does not teach away."

6 Did I read it correctly?

7 A Mm-hmm.

8 Q So we were talking about Wei
9 reference. Can you tell me Wei reference
10 represent which strategy under the strategy
11 you listed in your declaration?

12 MR. QIU: Objection, unclear.

13 BY MR. CHEN:

14 Q So let me explain.

15 In your declaration, you have B1,
16 B2, B4, B4 --

17 A Yeah, yeah.

18 Q -- strategies, right?

19 A Mm-hmm.

20 Q I think that's the -- and, I mean,
21 to be more specific, I think it's on the
22 page 19 of your declaration, and you have

1 listed Wei next to B2, right?

2 A Yes.

3 Q B2. So you are -- so I'm asking the
4 question, actually, I already answered.

5 Wei represent B2 strategy, correct?

6 A Mm-hmm.

7 Q Okay. Can you tell me, in Wei, is
8 there any statement in Wei specifically saying
9 that it tell a POSA not to try B1, B3, or B4
10 strategy?

11 A Well, I would have to look at the
12 complete thing really, at the complete
13 document, to find out whether there's any
14 specific mentioning. Like whether they say
15 that, I'm not sure. I'm not sure.

16 Q But sitting here today, you are not
17 aware of that statement in Wei that's
18 specifically saying, hey, don't try it. B2,
19 don't try it -- sorry, don't try B1, don't try
20 B3, don't try B4.

21 A Yeah, so I'm not sure. I'm not --
22 yeah, not aware of like anything arguing for

1 or against this.

2 Q Okay. Are you aware of any
3 statement in Wei that specifically say don't
4 try BA03 antibody?

5 A At least I can't remember anything
6 like that at this point.

7 Q Okay, yeah. I'm not trying to test
8 your memory. I'm just asking you, sitting
9 here today, are you aware of that statement in
10 Wei?

11 A Well, that's the same question. I'm
12 answering the same question. I don't remember
13 anything like that, you know.

14 Q Fair enough. Okay, I think that we
15 can talk about -- since we are talking about
16 strategy here, let's go to page 11 of your
17 declaration. I'm looking at the table. Yeah,
18 this table.

19 So there are five strategies here,
20 right: A, B1, B2, B3, B4. They're all from
21 the same reference; is that right?

22 A Well, I would -- I mean, the way

1 I've written this was I, I mean, basically
2 generated this table trying to summarize,
3 you know, all the different strategies.

4 I don't think I took it from a
5 specific reference. I could be wrong, but I
6 don't think so. I think that's what I did.

7 Q You cite -- you cite Exhibit 1009.

8 A Yeah, but I don't think -- yeah, but
9 what I did is try to summarize this for --

10 Q Right. But there's only one you
11 cite, right, 1009, and then you create this
12 table, you say strategy for addressing
13 anti-EGFR ADC.

14 Can I have a copy of 1009?

15 MR. CHOI: 1009?

16 MR. CHEN: Yeah.

17 BY MR. CHEN:

18 Q I think in paragraph 16 of your
19 declaration, you cite 1009, page 3.

20 A copy, Counsel, of 1009.

21 MR. QIU: Thank you.

22

1 BY MR. CHEN:

2 Q Here is 1009.

3 A Mm-hmm.

4 Q So page 3. Do you see that, page 3?

5 Where is it cited from? So you cite from
6 page 3, right? Yeah, here you cite it from
7 page 3.

8 Yeah, I think at the last paragraph
9 of the Exhibit 1009 is the strategy you were
10 talking about. Can you confirm that that's
11 the portion of the 1009 you cited for all the
12 strategies, right? The last paragraph -- no,
13 page 4, the top paragraph of page 4, yeah, it
14 says, "All of these strategies are aimed at
15 reducing toxicities toward skin and other
16 organs expressing EGFR, because currently
17 approved ... were deemed unsuitable for
18 development as immunoconjugates."

19 Okay, so this is the source you rely
20 on, right?

21 A What's the -- sorry, could you point
22 me to this, what you just read?

1 Q What I read is the top paragraph of
2 page 4.

3 A Page 4, all right.

4 Q Do you see that?

5 A Yeah.

6 Q It says, "All of these strategies."

7 A "All of these strategies," yeah.

8 Q So that's what you're talking about
9 in your declaration, right, the different
10 strategies; is that right?

11 A So that's what I'm talking about is
12 different strategies.

13 Q That come from this reference.

14 A As I said, so I think I tried -- I
15 remember I tried to summarize this, like what
16 I had in mind, the strategies. I didn't just
17 copy it from a document.

18 Q Okay.

19 A You know.

20 Q Okay. That's okay.

21 But the reference 1009 does not say
22 this is the only strategy that people can rely

1 on, right? They say there are some strategies
2 here, but they did not say -- the reference
3 does not say these are the only strategies
4 that can address safety issue, right?

5 MR. QIU: Objection, form.

6 THE WITNESS: Well, I'm not sure.

7 It does not say these are the only
8 strategies. Does it say these are the
9 only strategies? I don't think so.
10 Well, I don't think --

11 BY MR. CHEN:

12 Q You don't think?

13 A I don't think that that's what
14 they're saying, but I could be wrong. I mean,
15 again, I've developed this just to, you know,
16 get some -- provide some structure for the
17 different mechanisms that I had in mind, you
18 know.

19 Q Okay. So you summarized all these
20 strategies, right, from Exhibit 1009 to
21 address the safety concern, right, safety
22 concern?

1 A That was one of the -- one of the
2 results that I used, yeah.

3 Q Yeah, safety concern.

4 It doesn't address the efficacy,
5 right? This is just talking about safety.

6 A So it's talking about safety
7 concerns, yeah.

8 Q Right. You don't talk about
9 efficacy here, right?

10 A Not here in this table, for example,
11 no, I'm not talking about efficacy.

12 Q So for a therapeutic window or
13 therapeutic index, what are factors for
14 therapeutic window conjugate?

15 A Yeah, so the two main factors --
16 well, I don't really like the expression of
17 "therapeutic window." I would like give it a
18 different name, call it something like balance
19 between two factors or something.

20 Q Mm-hmm, right.

21 A You know, and it's basically the
22 dose of a drug -- or it's not just the dose,

1 but I would think the way you apply a certain
2 treatment within two limits that are set by,
3 you know, a minimum efficacy that you want to
4 see, and tolerable toxicity.

5 Q Okay.

6 A So, yeah.

7 Q Yeah, I think you state it in
8 paragraph 9 of your declaration. It basically
9 relate to two trends, right, efficacy and
10 toxicity, right?

11 A Mm-hmm.

12 Q But for therapeutic window, so the
13 strategy you list here is really only
14 addressing safety concern, like toxicity? You
15 don't really address efficacy, right?

16 A No, I don't, not here, that is
17 correct.

18 Q So what you address here, not
19 necessarily, you know, equivalent to
20 therapeutic window because you are not talking
21 about efficacy here, right?

22 A I would say -- well, it's not --

1 there's no factor that's equivalent to a
2 therapeutic window. I don't think that
3 there's anything -- any measure that's
4 equivalent to the therapeutic window.

5 I mean, it's always a combination of
6 things that in some will result in a
7 therapeutic window, yeah.

8 Q So for a drug, right, do you need to
9 consider absorption of a drug in order to --
10 for that drug to be effective?

11 A Did you say adoption?

12 Q Absorption.

13 THE REPORTER: Oh, absorption?

14 MR. CHEN: Yeah.

15 THE REPORTER: I'm sorry.

16 THE WITNESS: Absorption.

17 BY MR. CHEN:

18 Q Yeah.

19 A Well, let me -- I would have to
20 think for a minute.

21 Well, absorption is a mechanism. Do
22 you need to know it to determine, you know,

1 therapeutic window? Well, I'm trying to find
2 a setting where that would be the case. If I
3 think long enough, I'd probably find
4 something.

5 Q It's pharma 101.

6 A Yeah, right, but yeah.

7 You know, my opinion is that that's
8 not one of the most important factors,
9 I think, you know, but, well, people could
10 say, yeah, it will have an effect. It could
11 have an effect on the therapeutic window I
12 guess as well, yeah.

13 Q Okay. So efficacy definitely is
14 important, right?

15 A So efficacy is one way to -- that
16 contributes to the definition of the
17 therapeutic window.

18 Q What about metabolism?

19 A Well, it's the same thing as
20 absorption. You know, I don't think it's an
21 immediate -- immediate -- it's not an
22 immediate readout, basically, that will help

1 you to define the therapeutic window. Yeah, I
2 would say not an immediate factor, right, no.

3 Q Do you need to consider
4 pharmacokinetics of the ADC?

5 A For your therapeutic window?

6 Q Yeah.

7 A It depends really. Yeah, I would
8 think yes maybe. It depends on the drug and
9 the circumstances like entirely, so it's
10 really -- again, I think it's not -- I mean,
11 it's not an immediate factor, but it could
12 play a role as well, yes, of course. If the
13 drug stays around for a long time, it's very
14 toxic. You know, that could play a role, you
15 know.

16 Q But you did not talk about PK in
17 your declaration, right?

18 A No, no.

19 Q Let's go to your paragraph 91, 92 in
20 your declaration.

21 A Yeah.

22 MR. QIU: That's page 45.

1 MR. CHEN: That's page 45,
2 paragraph 91, 92.

3 THE WITNESS: Yeah.

4 BY MR. CHEN:

5 Q Okay. So this part I believe you
6 were saying that "Claim 13 further specifies
7 the cleavable linker as the vc linker and the
8 cytotoxic payload as MMAE."

9 And then you say, "Such a specific
10 ADC was tested in the experimental examples of
11 the '370 patent, referred to as MYK-3.
12 Against colorectal cancer cells, MYK-3
13 exhibited an inhibitory activity 'much higher
14 than those of monoclonal antibody BA03 itself
15 and BA03 plus free vcMMAE.'"

16 So, Doctor, I tried to understand.
17 This here you actually -- what he says, right,
18 he actually compared to -- compared the MYK-3,
19 which is ADC, right, BA03 ADC, compared the
20 BA03 ADC against the BA03 MYK antibody, right?
21 And then compared to BA03 plus the free, which
22 is not conjugate form, just like antibody plus

1 drug basically, right, the small molecule
2 basically.

3 So did you see -- did you find any
4 data in '370 that compare MYK-3 against
5 another ADC?

6 A I don't understand what the -- I
7 mean, I understand what you just read to me,
8 what this is about. I don't understand how
9 the question is related to this part. I don't
10 understand.

11 Q Yeah, so here -- let me explain.
12 I'm sorry about that.

13 So basically what you say here is
14 that you compared the BA03-vc-MMAE ADC, right,
15 called MYK-3?

16 A Mm-hmm.

17 Q You compared to the antibody
18 itself --

19 A Yes.

20 Q -- BA03. And you compared to --
21 BA03 mixed with MMAE is an unconjugated form.

22 So my question is, did you see any

1 data in the challenged patent that compared
2 the MYK-3 with another ADC?

3 MR. QIU: Objection, form.

4 THE WITNESS: I don't remember.

5 BY MR. CHEN:

6 Q Okay. Sitting here today, you are
7 not aware --

8 A I don't remember, sorry.

9 Q Sitting here today, you are not
10 aware of that kind of such data exists in
11 the '370 patent, right?

12 A So I'm not -- I don't remember any
13 of these, anything like that, but, you know, I
14 can't state -- I don't remember whether that's
15 addressed.

16 Q Okay, that's fine.

17 So there's no -- let me put it this
18 way. Wei disclosed ADC, right, the Y104D ADC,
19 that linked to vc-MMAE, correct?

20 A Yes.

21 Q Wei reference, right?

22 A Yes.

1 Q And then Leanna reference disclose
2 Antibody-1 conjugate to vc-MMAE, right?

3 So this '370 patent, in this patent,
4 do you see any data that actually compare
5 the BA03-vc-MMAE with the ADC that's disclosed
6 in --

7 A Leanna?

8 Q -- Leanna and ADC disclosed in Wei?
9 Did you see any data like that?

10 A No, I don't think I saw any data
11 like that.

12 Q That's fine. Okay, let's take a
13 look at -- go back to Exhibit 1009 again.
14 Exhibit 1009.

15 A Oh, sorry.

16 Q So Exhibit 1009, I think you also
17 cited in your declaration talking about
18 cleavable linker versus non-cleavable linker;
19 is that right?

20 A Yeah, I'm lost at the moment.
21 I'm sorry.

22 Q Okay. Are you still looking for

1 1009?

2 A 1009.

3 THE REPORTER: It's this.

4 MR. QIU: Yeah, this one you're
5 looking at, yeah.

6 MR. CHEN: Yeah, look at the bottom,
7 yeah.

8 BY MR. CHEN:

9 Q So you cited 1009 in your
10 declaration, right?

11 A Yeah.

12 Q And discussing the -- you know, the
13 linker type, right, cleavable/non-cleavable,
14 right?

15 And then I want you to take a look
16 at Figure 13. Figure 13 is on -- where is it?
17 Figure 13 is -- Figure 13 is page 42 all the
18 way -- okay.

19 Figure 13, and then I think we need
20 to look at the figure legend, I guess. Like
21 figure legend is where I think -- that's in --
22 yeah, that's in page 10. Page 10 is a figure

1 legend for Figure 13, okay?

2 Are you there, Doctor?

3 A Yes.

4 Q Yeah, open up page 10, right,
5 Figure 13.

6 A Yes.

7 Q So it says, "Figure 13 shows that
8 conjugation of cetuximab to MMAE
9 anti-microtubule payload by a cleavable
10 linker -- I'm sorry, I need to slow down.

11 THE REPORTER: That's okay, I'll
12 find it in the document.

13 BY MR. CHEN:

14 Q And the vc linker potentiates its
15 toxicity against both normal cells and
16 MDA-MB-468 cancer cells, and that's cetuximab
17 2C9-MMAE.

18 And, Doctor, you are aware that the
19 cetuximab 2C9-MMAE, 2C9 is a cleavable linker,
20 right?

21 A Yes.

22 Q That's a cleavable linker, okay.

1 And then it really compare to the
2 conjugation where a non-cleavable linker,
3 which is SMCC, right?

4 And then the -- again, this is a --
5 Doctor, it's on the top paragraph at page 11
6 now. I'm reading that, right? Page 11, on
7 the top paragraph --

8 A Yes.

9 Q Top paragraph, I'm reading that,
10 okay?

11 So it basically compare the
12 cetuximab 2C9-MMAE with -- another version is
13 a conjugation where "non-cleavable linker
14 (SMCC) only (cetuximab 2C9-DM1)," right?

15 So I try to understand, Doctor, is
16 that between cetuximab 2C9-MMAE and the one
17 called cetuximab 2C9-DM1, right, the linker
18 are different, right? One is cleavable
19 linker, the second one is non-cleavable
20 linker, SMCC.

21 And then you also look at the
22 payload. They are also different, right?

1 A (Witness nodding head yes.)

2 Q One is using MMAE, the other one use
3 DM1; is that right?

4 A Yes, I think so.

5 Q Okay. So scientifically, if you
6 have two variables, this is not a head-to-head
7 comparison, right? Linker is different, your
8 payloads are different. You can't do a very
9 scientific comparison, correct?

10 MR. QIU: Objection, form.

11 THE WITNESS: Let me take a quick --

12 BY MR. CHEN:

13 Q Yeah, sure, sure.

14 A Just go over the figure in more
15 detail, and then I'll --

16 Q Take a look.

17 A -- answer your question.

18 Okay, so ...

19 (Witness reviewing Exhibit 1009.)

20 Did you have this, like the y-axis?

21 I don't -- I can't read the y-axis, the

22 legend, like the title of the y-axis. Do you

1 have that? I don't know what it's --

2 surviving something something something.

3 Q Yeah, this is a -- I don't see that

4 either, but it's probably surviving a

5 fraction.

6 A Oh, fraction.

7 Q Surviving fraction.

8 A Okay.

9 Q It's basically the same --

10 A Oh, it's the same as --

11 Q Yeah, y-axis as the left panel.

12 A Do you have like information? I

13 mean, I'm just looking. I mean, I don't know,

14 for example, normal cells and tissue, which

15 one is which?

16 Q Look, I'm not necessarily asking you

17 to interpret the graph. I'm asking you the

18 figure legend of the Figure 13, right?

19 A Yeah.

20 Q And then it's really compared

21 between the two ADC, right? One use the

22 cleavable linker, the other use non-cleavable

1 linker, right? And then the payloads are
2 different; one is MMAE, one uses DM1. That's
3 all I'm asking.

4 And then this reference basically do
5 a comparison of these two constructs, right?
6 And I'm asking you, as a scientist, where you
7 have two variables in the two concepts you're
8 trying to compare, you know, how do you make a
9 head-to-head comparison if you have two
10 variables here?

11 MR. QIU: Objection, form.

12 THE WITNESS: That's exactly what
13 I'm trying to understand. You know, let
14 me go over this because, I mean, there
15 are -- just looking at this, there are
16 two versions of the cetuximab that use
17 the same payload, and I'm just trying to
18 understand what's the difference.

19 Oh, my God, I'm having a hard time
20 reidentifying these, yeah.

21 BY MR. CHEN:

22 Q Yeah, I don't -- is it correct that

1 I don't see Figure 13 has the cetuximab link
2 to MMAE using a non-cleavable linker, right?

3 A That's what I'm trying to determine.

4 Q Yeah.

5 A That's what I'm trying to find out.

6 I don't know. I mean, it has -- I
7 don't think it -- like, you know, I'm
8 looking -- I'm trying to understand what's the
9 difference between, for example -- first of
10 all, it's like impossible. I can't barely
11 read this.

12 Q Yeah.

13 A I can't see the -- you can't even
14 read this.

15 Q Right.

16 A I'm having a hard time identifying
17 these curves really, the identity of the
18 symbols.

19 And then I'm having a hard time
20 understanding because it's not saying in the
21 legend what's the difference between these two
22 cetuximabs with the DM1. What's the

1 difference between these two? I have no idea.
2 It doesn't say. It doesn't explain what that
3 is really, so ...

4 Q You don't see -- Figure 13, right,
5 you don't see a direct like head-to-head
6 comparison between a cetuximab conjugate to
7 MMAE using a cleavable linker compared to
8 cetuximab conjugate to MMAE using a
9 non-cleavable linker, right?

10 You don't see that, right?

11 A I don't see that unless this is
12 explained. I cannot -- you know, so the
13 legend does not explain everything that's
14 shown in the figure. It's a fact.

15 Q Yeah.

16 A I mean, these two things are not
17 explained. I do not know -- I don't know what
18 these two are really, what's the difference
19 between these two.

20 Q Okay.

21 A I don't know. So it's hard for me
22 to say.

1 Q Yeah, that's fair enough.

2 A It's hard for me to say.

3 Q No, I don't want you to find

4 something that hardly doesn't show up there.

5 I just wanted to confirm you don't see it, you

6 know.

7 So can you go to Exhibit 11 -- 2011

8 again? Exhibit 2011. So, Doctor, we have

9 three boxes there, so you're going to stay

10 here tonight.

11 A We have three more boxes?

12 Q Yes.

13 A That's great.

14 Q So earlier today you point me to a

15 table in the -- I think in this reference

16 that's on page -- I don't remember. Let me

17 see. It's page 26, I believe, if I still

18 remember that. Yes, page 26, I remembered

19 correctly.

20 You point me to that Table 4, right?

21 And this table listed antibodies, a number

22 of -- several antibodies, including 6/LC

1 antibody, correct?

2 A Yes.

3 Q Right? This is the one with the
4 antibody this reference disclose, right?

5 A Mm-hmm.

6 Q And then in the Table 4-1 on the
7 next page, you see that the 6_LC is listed in
8 the table again, right?

9 A Yes.

10 Q So the KDs are 250, right?

11 A Yes.

12 Q KD 250, is this low affinity
13 binding, or is it high affinity?

14 A Well, I think that's probably,
15 comparably, high affinity I'd say.

16 Q It's a high affinity?

17 A No, no, I'm sorry.

18 Q Low?

19 A Low, yeah.

20 Q Low, right?

21 A Yeah.

22 Q Yeah. So it's micromolar, almost

1 like micromolar.

2 A Yeah.

3 Q It's lower.

4 So you cited this reference for
5 Strategy B4, right, for the low-binding
6 affinity antibody, correct? So 6/LC is one of
7 them, right, low-binding affinity antibody?

8 A I think so.

9 Q Okay, so low-binding affinity, okay.

10 So, Doctor, I want you to go to
11 page -- hold on a second -- page like 11 of
12 Exhibit -- oh, sorry, I have to mention.
13 Let's turn to Exhibit 1009. You can put away
14 that one. I'm not going to use that one.

15 A Okay.

16 Q Now let's look at Exhibit 1009
17 again.

18 A 1009, that's that one.

19 Q Yeah, these two references are
20 published from the same lab, right,
21 Tikhomirov? Yeah, can you find that? 1009.

22 Can you go to page 11 of this

1 reference, Exhibit 1009? So page 11 of --
2 remember when I'm talking about page, it's
3 stamped page, not the actual page numbers. I
4 don't want you to go to look at the --

5 A Yeah.

6 Q So page 11, on the bottom, right, I
7 want to read that sentence, okay?

8 So, "By this measure, and as shown
9 in Figure 9, at least the following known
10 antibodies are not suitable for use in the
11 present immunoconjugates," right?

12 And then it says, "J2898A,
13 intellimab 6-LC," right? And then
14 parentheses, this is a cetuximab variant
15 taught in WO 2012/100346, and that actually is
16 Exhibit 2011, right? And then the next
17 antibody is nimotuzumab, and matuzumab.

18 So, Doctor, you see that statement
19 from the Exhibit 1009, right? So the -- that
20 the antibody that -- the known antibody that
21 are not suitable for the present
22 immunoconjugate, including the 6-LC, that 6-LC

1 antibody that's disclosed in Exhibit 2011,
2 correct, and also including --

3 A I guess so.

4 Q Right, including the one nimotuzumab
5 that we know earlier has a favorable, you
6 know, toxicity profile based on Crombet
7 reference.

8 So my question is that, even for
9 Strategy B4, there's no necessarily, you know,
10 work, right? Sometimes it work, sometimes --
11 maybe sometimes doesn't work; is that correct?

12 A No, I --

13 MR. QIU: Objection,
14 mischaracterizes document.

15 BY MR. CHEN:

16 Q Okay, not suitable.

17 A Yeah, can you --

18 Q Not suitable. So this statement --
19 I tried to understand this statement here,
20 right? It's basically saying that the 6-LC
21 antibody is not suitable for use in the
22 present immunoconjugate, correct?

1 MR. QIU: Objection,
2 mischaracterizes document.

3 BY MR. CHEN:

4 Q I'm just reading that.

5 So what it says, right, at least the
6 following known antibody, right, including
7 6-LC from the Exhibit 2011, are not suitable
8 for use in the present immunoconjugate, right?

9 Did I read that correctly?

10 A Yes.

11 Q Okay. So the 6-LC antibody is the
12 one you cited for B4 strategy, right?

13 MR. QIU: Objection,
14 mischaracterizes testimony.

15 THE WITNESS: Can you repeat?

16 Sorry.

17 BY MR. CHEN:

18 Q Earlier we talk about that, right,
19 the 6-LC. We established that 6-LC is the
20 low-binding affinity antibody, right? And
21 that is, according to your Strategy B4, one of
22 the antibodies, you know, meet this criteria

1 for B4. It's a low-affinity antibody.

2 MR. QIU: Same objection,
3 misrepresents testimony.

4 THE WITNESS: Let me take a look at
5 this again.

6 So we're combining -- what we're
7 doing is -- I mean, what he's talking
8 about is something else. It's not
9 affinity, right? He's not talking about
10 affinity, per se. He's talking about
11 something else.

12 BY MR. CHEN:

13 Q I'm not asking that. I'm just
14 asking to confirm that, you know, at least
15 what it says here, is that the 6/LC antibodies
16 are not suitable for the present
17 immunoconjugates. That's what it says, right?

18 A I mean, what he -- yes, but he's
19 saying that because of the agonist activity of
20 the antibodies. That's what he's addressing
21 in this paragraph, right?

22 Q Sure.

1 A So you're referring, I mean, to

2 B4 --

3 Q Right.

4 A -- but he's actually referring to a
5 different strategy. He's referring -- in the
6 end, he's referring, for example, to the
7 cleaver -- cleavable linker.

8 Q Linker, right?

9 A Linker, yeah.

10 Q So I guess you are right. I mean,
11 there are different strategies, right?

12 A Yeah.

13 Q So the one you refer to is
14 addressing safety issue, and here it's a
15 different strategy?

16 A Yes. So he's saying -- what he's
17 saying -- he's not referring, I think, to --
18 in this paragraph, he's not referring to
19 affinity at all as a quality of the antibody.
20 He's only referring to the agonist or
21 antagonist activity of the -- of the antibody.

22 Q So the same antibody, such as 6-LC

1 antibody, may not be suitable under one
2 strategy, but can be used for a different
3 strategy, is a fair statement?

4 A I think --

5 MR. QIU: Objection, incomplete
6 hypothetical.

7 THE WITNESS: Well, if you leave
8 these examples out, I would say if you
9 just look at the table, you could say,
10 yeah, you know, you don't need to fulfill
11 all the criteria as long as you -- that
12 some of these criteria is acceptable.

13 BY MR. CHEN:

14 Q Mm-hmm.

15 A Yeah.

16 Q I try tried to understand this
17 better. Earlier you say 6-LC really is the
18 one you mentioned for B4 strategy.

19 And then here, based on what you say
20 under different strategy, 6-LC antibody is not
21 suitable for this reference, the strategy
22 under this reference, right?

1 A Yeah.

2 MR. QIU: Objection,
3 mischaracterizes.

4 BY MR. CHEN:

5 Q That's why I kind of try to ask you
6 to confirm, you know. So same antibody --
7 that is, 6-LG antibody -- can be suitable for
8 one strategy, but not necessarily suitable for
9 another strategy, is a fair statement?

10 A No.

11 MR. QIU: Objection --

12 MR. CHEN: No?

13 MR. QIU: -- mischaracterizes
14 testimony.

15 THE WITNESS: That's not what I'm
16 saying.

17 BY MR. CHEN:

18 Q Okay. Then what did you say?

19 A I think, you know, what I'm saying
20 is I'm defining the outcome as you could say
21 applicability of the antibody.

22 Q Mm-hmm.

1 A And what I'm saying is you have
2 these factors that are characteristics of the
3 antibodies, and in combination, they will
4 define, you know, the potential applicability
5 of the antibody.

6 So it's not just one yes and one no
7 or something, but it's multifactorial. Like,
8 you know, to a certain degree, this factor
9 will come in.

10 Q Right.

11 A To a different degree, the other
12 different factor will come in, and then
13 hopefully you'll have an outcome justifying
14 the application.

15 Q So you are saying that one should
16 not just consider -- only consider binding
17 affinity, right? You have to consider other
18 factors as well?

19 A I mean, that's what the table shows,
20 right? I mean, it's not just one factor.

21 Q Right, right, okay.

22 Okay, let's move on to next subject.

1 Okay, let's go to paragraph 85 of
2 your declaration.

3 THE REPORTER: Page 42.

4 THE WITNESS: Page 42?

5 BY MR. CHEN:

6 Q Page 42, paragraph 85, yeah.

7 Are you on that?

8 A I'm sorry.

9 Q Sorry, it's a long day, and we try
10 to go through lots of stuff.

11 A Yeah, I know.

12 Q Yeah, so paragraph 85 again.

13 A I'm sorry.

14 Q Your declaration.

15 Counsel, can you help --

16 A So stupid.

17 MR. QIU: Yeah, sure.

18 MR. CHEN: -- the doctor to find his
19 declaration? He can --

20 MR. QIU: Here.

21 MR. CHEN: Yeah, he'll put away all
22 his stuff. Here we go, page 42.

1 THE WITNESS: All right, page 42.

2 BY MR. CHEN:

3 Q Yeah.

4 A 85, yeah.

5 Q Okay. So what you say is there are
6 a number of trials of ADC -- anti-EGFR ADC
7 failed, is that right, including --

8 A A number of trials of what?

9 Q Of anti-EGFR ADC, right?

10 A Yeah.

11 THE REPORTER: Where are you
12 reading? I'm sorry, I can't understand
13 the letters you're saying.

14 BY MR. CHEN:

15 Q Anti-EGFR ADC failed, okay.

16 And then in the -- you know, in the
17 last sentence of paragraph 85, okay, you says
18 that, "However, 'enrollment in [a phase II/III
19 study] has been halted since 2019 due to lack
20 of survival benefit for patients receiving
21 ABT-414,'" right?

22 A Mm-hmm.

1 Q The ABT-414 is what? It's an
2 antibody binds to EGFR variant 3, right?

3 A Yes.

4 Q It's a mutant form of EGFR, right?
5 Okay, that trial was terminated.

6 So the reason is a lack due to --
7 you say that due to lack of a survival
8 benefit, right?

9 A (Witness nodding head yes.)

10 Q That's efficacy, right? That's due
11 to efficacy?

12 A That's one --

13 MR. QIU: Objection, compound.

14 THE WITNESS: That's one --

15 BY MR. CHEN:

16 Q Reason?

17 A Measure of efficacy.

18 Q That's right, okay.

19 And then you measure in your
20 paragraph 87, so there's another ADC from
21 AbbVie called ABBV-221. So you say in that
22 the trial, Phase I study of ABBV-221, has

1 reportedly been terminated, right?

2 Do you know the reason why?

3 A I was wondering, but I haven't been
4 able to, you know, determine the reasons for
5 all the different, you know, antibodies, yeah.

6 Q We don't know if it's because of
7 safety reason, or could be efficacy reason?
8 We don't know.

9 A So I think the information is
10 probably out there, but I haven't determined
11 individual reasons.

12 Q Okay. So going to paragraph 88, so
13 you're talking about another ADC called
14 ABBV-321, right? So it says, "Nevertheless,
15 no further phase 2 or 3 testing has been
16 reported, suggesting that its development has
17 been terminated," right?

18 A (Witness nodding head yes.)

19 Q Again, do you know the reason of the
20 termination?

21 A No, I don't.

22 Q Okay. And then next paragraph,

1 paragraph 89, you are talking about HTI-1511.

2 So you say that the halozyme reported a
3 preclinical testing of HT1 -- sorry, HTI,
4 actually -- HTI-1511 in 2016.

5 And then you continue saying they're
6 suggesting that the pH-selective antibody,
7 like the pH-selective antibodies of Wei,
8 right, the antibody in HTI-1511.

9 And then I jump ahead to say the
10 last sentence of this paragraph 89, "Since
11 2016, however, there has been no report of
12 clinical testing for HTI-1511, suggesting that
13 its development has been terminated."

14 Do we know the reason of
15 termination?

16 A I don't personally. I don't.

17 Q So in your table in paragraph 86,
18 you listed -- it lists like three ABT -- or,
19 sorry, the three program, ADC program, from
20 AbbVie which use antibody that specifically
21 binds to EGFR variant 3, has been terminated,
22 right? At least one of them you know is due

1 to efficacy reason. The rest of them we don't
2 know.

3 And then for the last one, halozyme
4 trial, this halozyme antibody you mentioned is
5 a pH-selective antibody, right?

6 A (Witness nodding head yes.)

7 Q So if I understand correctly, the
8 first three is a B1 strategy?

9 A Mm-hmm.

10 Q And then the halozyme is a B2
11 strategy that binds to a mutant form of EGFR,
12 right?

13 A (Witness nodding head yes.)

14 Q So according to your strategies, B1,
15 B2, there's still -- they can fail, right?
16 The program can still fail? No guarantee
17 they're going to win -- they're going to
18 succeed?

19 A Yeah, there's no guarantee.

20 Q Right. They can still fail, right?

21 A Yeah, I mean, that's what the data
22 are indicating.

1 Q Right. So people looking at the
2 data, they will understand, even there's a B1,
3 B2, B3, B4, and A strategy, you follow them,
4 you don't necessarily get successful ADC,
5 right?

6 A A successful -- but that's not what
7 I -- I didn't say like if they fulfill all the
8 criteria, everything looks perfect perfect.
9 It can still fail.

10 Q Yeah.

11 A What these did is they, as far as I
12 know at least, they addressed one of the
13 criteria. I don't know about the other
14 criteria.

15 And as I just explained, I mean,
16 this is the table. I've never said it's a yes
17 or no, you need to fulfill this one thing,
18 then everything is going to be fine.

19 Q Yeah.

20 A The other thing, you know, you don't
21 care.

22 But it's true, each one of them

1 addressed one of the -- at least one of the
2 criteria, and they still failed.

3 Q Right.

4 A But that just confirms my theory, my
5 opinion, that it's a mixture of all these
6 things that matter.

7 Q Right, right, right, right.

8 So, obviously, the program can be
9 terminated not just because of safety? Can
10 be --

11 A No, yeah, absolutely.

12 Q Right?

13 A Yeah, there could be a number of
14 reasons.

15 Q Right. But in your declaration,
16 your strategies focus on the safety issues?

17 A Yes, I decided to focus on safety
18 for a reason, and the reason is that I think
19 that's the primary criterion for any drug is
20 safety, so that's the number one question.

21 Q Efficacy is also equally important?

22 A No, it's not equally important.

1 That's why the FDA asks you to do a Phase I
2 first, is because they want to see -- make
3 sure it's safe. Yeah, safety comes first, and
4 I think that's why -- you know, I think that's
5 more important.

6 And also, as a physician, you're
7 supposed to -- number one rule is not to help
8 the patient. Number one rule is not to cause
9 harm.

10 Q Yeah.

11 A Right, that's the number first rule.

12 Q Obviously, in Phase I you test
13 safety, but preclinical, you do know the
14 antibody, or ADC, has efficacy, right?

15 A Yeah, right. Yeah, right.

16 Q You have to know --

17 A So I'm not saying you don't take
18 that into account.

19 Q You have to know the antibody is
20 effective before you test the safety in human.

21 So can you bring the Patent Owner
22 Response again? Patent Owner Response.

1 I think, Doctor, you have a copy of that.

2 A I have everything.

3 Q Yeah, you have everything, right, so
4 can you go to Patent Owner Response?

5 Declaration, I don't need that one.

6 Where is it? Oh, here we go.

7 MR. QIU: Counsel, by the way, I
8 realize that there are highlighting in
9 the Patent Owner Response that you bring.

10 MR. CHEN: The highlight, right?

11 MR. QIU: Yeah. That's something
12 you added, right?

13 MR. CHEN: Yeah, we added the --
14 yeah. I think like what you say is more
15 like colloquial. You know, we forgot to
16 remove the highlight, yeah, but we did
17 not modify the content at all.

18 BY MR. CHEN:

19 Q So let me see. Okay, Doctor, could
20 you go to page 62?

21 So 62, I just wanted to read the
22 subheading. I think the Patent Owner here

1 alleged that Petitioner considered different
2 approaches in creating the anti-EGFR ADC and
3 chose to copy ADC claimed by '370 patent,
4 right? Did I read that correctly?

5 So what is the exhibit for that
6 Patent Owner's application then? Where's that
7 application? Do you remember?

8 Okay, I think Exhibit 2008 -- do we
9 have a copy? Okay, Counsel.

10 MR. QIU: Thanks.

11 BY MR. CHEN:

12 Q So this is an application you cite
13 in your reference. Basically it's from
14 Petitioner's, like, application, and we talk
15 about this. This is a post-filing
16 application, and I want you to go to page 35,
17 right?

18 So in your declaration, I believe
19 you mentioned several ADC created by
20 Petitioner, including in the Table 1 here,
21 SWY2110, 2111, 2112, and 2113, right?

22 A Mm-hmm.

1 Q So can you take a look at the
2 chemical structure in paragraph 154 here?

3 Can you tell me, is this small
4 molecule, is that cytotoxic agent, is that
5 molecule an MMAE or not?

6 A That's -- well, I would say no, not
7 in a reliable way. So I'm not a chemist. I'm
8 not able to give you a sufficiently qualified
9 answer on that, no.

10 Q Okay, fair enough. Okay, let's put
11 aside that document.

12 Do we want to take a quick break?
13 Like how long have we've been going?

14 MR. QIU: Sure.

15 THE VIDEOGRAPHER: An hour and
16 11 minutes.

17 MR. CHEN: Okay, that's -- would it
18 be okay with you?

19 MR. QIU: Yeah, let's take a break.

20 MR. CHEN: Yeah, quick break, go at
21 that bathroom and -- yeah.

22 MR. QIU: Yeah.

1 THE VIDEOGRAPHER: The time is
2 3:26 p.m. We're now off the record.

3 (A break was taken.)

4 THE VIDEOGRAPHER: The time is
5 3:34 p.m. We are now on the record.

6 BY MR. CHEN:

7 Q Okay, welcome back.

8 So I just have a follow-up question
9 on the paragraph 86 of your declaration.

10 A Mm-hmm. Paragraph 86, yeah.

11 Q 86, right.

12 So there are three programs listed
13 as EGFRvIII, right?

14 The Antibody 1, does it also bind
15 specifically to EGFRvIII as well?

16 A Yes, as far as I know, yeah, it
17 does.

18 Q Okay. All right.

19 Doctor, could you go to paragraph 70
20 of your declaration?

21 A Yes.

22 Q So here you say that, "The BA03

1 antibody is a humanized derivative of
2 cetuximab. Cetuximab has a well-recognized
3 ability to also bind to EGFR expressed on
4 normal cells, leading to toxicity," right?

5 And then you continue stating that,
6 "The BA03 antibody, therefore, would have been
7 expected to have the same binding activity to
8 tumor and normal cells."

9 So you did not cite to any
10 scientific reference, right? So what's the
11 data you rely on for this statement?

12 A I would say -- so you're referring
13 to this sentence?

14 Q That sentence, yeah.

15 A "[W]ould have been expected to have
16 the same binding activity to tumor and normal
17 cells"?

18 Q Yeah.

19 A I think if I'm correct, what that
20 was supposed to mean is the same binding
21 activity as cetuximab, the same binding
22 activity to both tumor cells and normal cells,

1 yeah.

2 So I'm not saying -- I don't think
3 that that's -- well, I think that was the
4 true -- that was the meaning of this -- that's
5 what it was supposed to mean, yeah.

6 Q I guess I want to try to understand
7 what's the basis for that.

8 You're saying that BA03 has the same
9 binding affinity to tumor and normal cells.

10 What's the basis for that?

11 A So that's why I'm -- that's why I
12 was saying I don't think we're saying --
13 I think what we're saying is -- yeah, so just
14 like -- let me put it in different words.

15 Just like cetuximab, it's not able
16 to discriminate between healthy and tumor
17 cells to a degree that would be comparable,
18 for example, to the antibody from Leanna that
19 is able to discriminate, you know, more or
20 better.

21 Q But the -- so what does that
22 translate into? Like a narrower therapeutic

1 window compared to Leanna, Antibody 1?

2 A Well, yeah, that's -- you know, you
3 would have thought. So that's my opinion is
4 that a POSA would have thought that this
5 characteristic -- that's one of the
6 characteristics. The inability of the
7 antibody to discriminate between normal
8 tissues and healthy tissues, that that's one
9 factor that would predict higher toxicity.

10 Q But in order to compare therapeutic
11 window between two ADC, for example, if you
12 want to compare the cetuximab ADC to
13 Antibody 1 ADC, you need to know both efficacy
14 and toxicity, correct?

15 A If you want to like have all the
16 information that you can get to determine the
17 most accurate therapeutic window --

18 Q Yeah.

19 A -- I think you would need more than
20 just one fact, more than just toxicity, yes.

21 Q Right. You need to also know the
22 efficacy --

1 A Yeah, and that's --

2 Q -- by a POSA?

3 A I've provided you with a
4 definition -- with my definition of
5 "therapeutic window," and it's in there, you
6 know, yeah.

7 Q But cetuximab has excellent
8 efficacy, right?

9 A Well, that's -- yeah, all I -- I'm
10 not saying, but, yeah, I would say it's
11 efficacious, right? So I'm not in a position
12 to judge on like excellent -- whether that's
13 excellent or not, yeah.

14 Q So cetuximab was proved more than
15 20 years ago, right?

16 A (Witness nodding head yes.)

17 Q So it has been used for a couple
18 decades already by now, right? Yeah.

19 A (Witness nodding head yes.)

20 Q So going back to that statement, I'm
21 still trying to understand here "the same
22 binding activity."

1 So I think in your declaration, I
2 see different terms, right? Earlier we're
3 talking about binding affinity, right? We're
4 talking about the BA03 relative to cetuximab
5 binding affinity. Now you are talking about
6 binding activity.

7 What's the difference between
8 binding activity and binding affinity?

9 A So what I'm addressing here is the
10 tumor specificity of the antibody, and so
11 that's the title of the --

12 Q Okay.

13 A -- of the -- of this chapter, right?

14 And I'm comparing an antibody that's
15 more tumor specific because it's targeting a
16 variant that's only expressed in tumor cells
17 to -- to a very -- to actually two antibodies
18 that do not have this type of specificity
19 because they target wild-type EGFR.

20 Q I see. So my understanding, if I
21 understand correctly, is that you're comparing
22 to Leanna Antibody 1. So Leanna Antibody 1

1 binds specifically to EGFRvIII, and cetuximab

2 binds to wild-type EGFR, correct?

3 A (Witness nodding head yes.)

4 Q Is that right?

5 A Yeah, that's correct.

6 Q Okay. But in Crombet reference

7 earlier, we were talking about EGFR have

8 different copy numbers, right?

9 On the tumor cell, you know, Crombet
10 assumed to be 106 cells, number on the cell,
11 and then on the normal cell, it assumed to be
12 104, right, which translate into 100 times,
13 100-fold, right, more EGFR on tumor cell
14 versus normal tissue.

15 Would that contribute to like for
16 antibody to differentiate normal cell versus
17 tumor cell?

18 MR. QIU: Objection, form.

19 THE WITNESS: Yeah, I would say
20 it -- the expression levels of the target
21 antigen, to some degree, they contribute
22 to the -- well, it's obvious, I mean, to

1 the overall binding.

2 BY MR. CHEN:

3 Q Mm-hmm.

4 A Or possibly, but not necessarily, to
5 the antibody's activity, however you want to
6 define them. But, yeah, it's a contributing
7 factor, and that's what I'm saying in my
8 declaration is that it is expressed on --
9 overexpressed on tumor tissues, and that's
10 what we've discussed before, so that's not
11 new, so yeah.

12 Q Yeah, what I'm missing is more about
13 the degree. I understand, you know, wild-type
14 EGFR is expressed on tumor cell and also
15 normal cell; and antibody, like a cetuximab,
16 can bind to EGFR on the normal cell and tumor
17 cell. I'm talking about the proportion or the
18 degree.

19 So if you have EGFR copying number
20 almost like 100-fold than normal cell, so the
21 impact -- you say, okay, impact on the EGFR
22 tumor cell, the binding, the degree is

1 different, right? There's more with respect
2 to higher degree or higher proportion on tumor
3 cell rather than versus from normal cell?

4 MR. QIU: Objection, unclear.

5 BY MR. CHEN:

6 Q Correct?

7 A Yeah, I would think you could say
8 that's what you would hope for is that that's
9 the case with an overexpressed antigen, right,
10 yeah.

11 Q Right, right.

12 A Yeah.

13 Q Yeah. So for the Antibody 1, which
14 binds to EGFRvIII, right, do you aware that --
15 are you aware that not all patients, like
16 cancer patients, have that variant 3 variant?

17 A Yes.

18 Q Only small -- a portion of patients
19 have that, right?

20 A Yeah, it's not all of the -- all the
21 patients that have this variant, yeah.

22 Q Do you -- are you aware at what

1 percentage, roughly?

2 A No, I don't -- I don't have like a
3 definite number.

4 Q But it's a -- it's a portion of the
5 population, patient population, has that EGFR
6 variant, right?

7 A (Witness nodding head yes.)

8 Q And then are you aware that the --
9 that even that variant can disappear during
10 recurrence?

11 MR. QIU: Objection.

12 MR. CHEN: Are you aware of that?

13 MR. QIU: Objection, assumes facts
14 not in evidence.

15 THE WITNESS: That's something --
16 well, first of all, I don't think that
17 that's relevant, really, at all to any of
18 the questions, but -- and also, I think
19 that's something that -- if I remember
20 correctly, it's something that's under
21 investigation still: when do these and
22 for how long do they persist, and when do

1 mutations occur, under what
2 circumstances?

3 So I think that's some -- first of
4 all, I think that's like something that's
5 out of scope for me and this question.

6 BY MR. CHEN:

7 Q Yeah, yeah.

8 A I'm not sure.

9 Q I mean, my question is yes or no.
10 If you're not aware of that, it's okay to say
11 no.

12 A No, yeah, I'm aware of the fact
13 that --

14 Q You are aware of that?

15 A -- those issues occur.

16 Q Yeah. You're aware that sometimes
17 EGFRvIII can disappear, right?

18 A Well, I'm not sure whether that's
19 actually the case. I'm not sure. I'm not
20 sure. I don't know. I'm not sure.

21 Q Okay, I just tried to confirm. You
22 are not aware of that -- that stuff, right?

1 A Well, yeah. Well, no.

2 Q Okay. So since the Leanna
3 Antibody 1 only binds to EGFRvIII, which only
4 account for a portion of patient population,
5 if a person skilled in the art want to target
6 a broader population, that person skilled in
7 the art will not use Leanna Antibody 1, right?

8 MR. QIU: Objection, form.

9 THE WITNESS: So that's a question I
10 cannot answer for a variety of reasons.

11 First of all, I cannot say whether
12 that's something that someone would or
13 would not do in reality. That's not
14 something that I can judge on. It's
15 impossible for me.

16 And also, as we've said before, none
17 of this is really like yes or no,
18 I think. It's all relative, I think.

19 So this question, the way you put
20 it, say, well, this is not something that
21 someone would do, it's not something
22 that -- I cannot answer that question.

1 BY MR. CHEN:

2 Q Okay, let me put it a different way.

3 Do you agree that that limit breadth
4 of targeting only a portion of population of
5 Leanna Antibody 1 is a limitation, right?

6 MR. QIU: Objection, form.

7 THE WITNESS: I would say -- well,
8 it depends on what limitation you're
9 talking about. Limitation of what?

10 BY MR. CHEN:

11 Q Meaning this antibody can only
12 target a portion of patient population, is
13 that considered to be a limitation?

14 A Well, there are so many --

15 MR. QIU: Objection, form.

16 THE WITNESS: -- unknowns.

17 I don't have that information. I
18 don't know whether this antibody only
19 targets, you know, this one mutation, or
20 whether it targets the wild type to some
21 degree. I don't have that information.

22 You know, in clinic -- I mean, for

1 clinic, if you ask me about clinical
2 applicability, I don't have that
3 information to answer that question to
4 give you a reliable answer to that
5 question.

6 BY MR. CHEN:

7 Q But Antibody 1 is specifically
8 targeting variant 3, right?

9 MR. QIU: Objection, asked and
10 answered.

11 THE WITNESS: Yeah, so that's the
12 purpose. I think that was what it was
13 invented for and designed for.

14 BY MR. CHEN:

15 Q So you only target -- we established
16 that variant 3 only express in a portion of
17 patient population, correct?

18 A Yeah, that's what we said before.

19 Q So therefore, I'm saying the
20 Antibody 1 only can target a portion of
21 population?

22 MR. QIU: Objection, asked and

1 answered.

2 BY MR. CHEN:

3 Q Patient population, yeah.

4 A Yeah, I've answered this before.

5 I don't have that information.

6 There could be -- I mean, there could be
7 alternative explanations. So I don't have
8 that information, whether -- I don't know
9 whether that's accurate, you know, the
10 targeting.

11 Q Yeah, but even if you don't have
12 data to see that, but based on the definition,
13 right, if you have an antibody only target a
14 specific mutation, which is a variant 3
15 mutation, it only work for that mutation,
16 right?

17 MR. QIU: Objection, asked and
18 answered.

19 THE WITNESS: I've answered -- I've
20 tried to this answer this before several
21 times. I don't have anything else
22 really.

1 BY MR. CHEN:

2 Q Okay, Doctor, could you go to
3 paragraph 63 of your declaration?

4 A Mm-hmm.

5 Q So, actually, Doctor, I want to
6 continue on this question earlier.

7 Can you go to paragraph 33?

8 A 33?

9 Q Yeah.

10 A Yes.

11 Q Okay, so I'm going to read that, 33.

12 "Leanna (Ex-1006) is another primary
13 prior art reference cited in the Petition. In
14 Leanna, the antibody in anti-EGFR ADC is
15 Antibody 1, which is a humanized version of
16 the antibody MAb806 mentioned in Tikhomirov.
17 MAb806 targets a mutant version of the
18 wild-type EGFR [which] is only expressed in
19 tumor cells," right?

20 So we mentioned earlier it's the
21 version 3.

22 MR. QIU: Counsel, are you reading

1 paragraph 63?

2 MR. CHEN: 33, 33.

3 MR. QIU: Oh, 33.

4 MR. CHEN: Right.

5 BY MR. CHEN:

6 Q So here you -- let me continue
7 reading. Are you on 33?

8 A Yes, I am.

9 Q "Since only 'the tumor expresses the
10 truncated version of the EGFR de2-7' ...
11 Antibody 1 does not bind to normal cells, and
12 thus avoids the safety concerns associated
13 with cetuximab. The antibody of Leanna,
14 therefore, is consistent with Strategy B1
15 outlined above," right?

16 So you stated here Antibody 1 does
17 not bind to normal cells, correct?

18 A Yeah.

19 Q Only binds to that mutant form,
20 which is EGFRvIII, correct?

21 A That's what I'm saying here.

22 Q Right.

1 A That's what you just read.

2 Q And that EGFRvIII only containing a
3 portion of population, patient population,
4 right?

5 A Again --

6 MR. QIU: Objection, asked and
7 answered.

8 BY MR. CHEN:

9 Q Okay. Correct?

10 A Yeah.

11 Q You have to say it.

12 A Yes, which I've said that before.

13 Q Okay. Let's go to paragraph 63 now.

14 Okay, so the last sentence of -- not
15 last sentence. The last sentence of the page,
16 page 32, okay?

17 A Mm-hmm.

18 Q And then go -- "To the extent the
19 increased EGFR phosphorylation inhibition
20 activity of the BA03 antibody could increase
21 the ADC's killing of the tumor cells, when the
22 ADC binds to a normal cell, however, such

1 increased EGFR phosphorylation inhibition
2 activity would also translate into higher
3 killing of the normal cells, leading to
4 toxicity. The parallel changes of the ADC's
5 killing activity against tumor and normal
6 cells, therefore, would mean no change to the
7 ADC's therapeutic window."

8 Did I read it correctly?

9 A Yes.

10 Q Okay. So you mentioned parallel
11 changes, right? Parallel changes.

12 A (Witness nodding head yes.)

13 Q Do you mean exactly same degree, or
14 is it a different degree between tumor cells
15 and normal cells?

16 MR. QIU: Objection, unclear.

17 THE WITNESS: Yeah, I don't think --
18 I'm not even addressing this. I'm just
19 saying it happens in parallel.

20 BY MR. CHEN:

21 Q In parallel.

22 A In parallel. That doesn't mean like

1 it's the same extent or anything, you know.

2 I'm just saying it happens at the same time

3 or -- you know.

4 Q So it's not necessarily the same
5 degree for the normal cell/tumor cells?

6 A I would say not necessarily, but
7 could be. I mean, I can't rule this out. I'm
8 just -- I'm not --

9 Q You don't know?

10 A That's not part of the statement. I
11 don't -- yeah.

12 Q But you draw a conclusion there's no
13 change to the ADC's therapeutic window, so
14 there has to be the same degree, right?
15 Because if you have parallel change on both --

16 A Yes.

17 Q -- tumor cell and normal cell, then
18 the implication is that --

19 A Yeah, right.

20 Q -- the changes are in the same
21 extent, same proportion, same degree?

22 A Yeah, right.

1 Q You agree, right?

2 MR. QIU: Objection,
3 mischaracterizes testimony.

4 THE WITNESS: I would say, you know,
5 in principle, I mean, one would have to
6 define really what "no change" means, to
7 what degree, you know.

8 I mean, you know -- yeah, well, it's
9 really like is it no change or minimal
10 change, or like when -- like what's the
11 cutoff? Like it's hard -- I would say,
12 you know, one would probably -- well,
13 I think also therapeutic -- as we just
14 said, the therapeutic window is
15 defined -- that's a clinical definition,
16 right?

17 So I would say, as it says here,
18 that's -- I mean, you have these parallel
19 changes in -- of killing activity, and
20 that could theoretically mean that
21 there's no major change in the
22 therapeutic window, but that would remain

1 to be determined.

2 BY MR. CHEN:

3 Q So you're not -- there's a --

4 MR. QIU: Objection,
5 mischaracterizes testimony.

6 THE WITNESS: Yeah, no, I think
7 it's -- it's -- no, you don't know when
8 you first -- yeah. We're developing
9 this, the whole thing, you don't -- you
10 don't have that information, I think. I
11 don't know.

12 BY MR. CHEN:

13 Q So just to be clear, so are you
14 saying that you don't know whether or not
15 there will be major change in the therapeutic
16 window, or no change?

17 In your declaration, you are saying
18 that there's no change to the ADC therapeutic
19 window.

20 A So what I would think -- say -- like
21 what I would say is, based on these -- on
22 these effects, on the effect of -- on normal

1 cells and tumor cells, I would say the --
2 well, the antibody has toxicity, or is toxic,
3 and has the same biologic effect on tumor
4 cells and healthy skin cells, so a similar
5 effect.

6 Q Yeah.

7 A And that can mean -- again, I'm
8 focusing, as you said, on toxicity, so I think
9 that this is not a solution to the toxicity
10 problem is the -- you know, the increased --
11 the antagonist, like an improved antagonist
12 function will not solve that problem, or a
13 high antagonist function. On the contrary,
14 possibly, you know, yeah.

15 Q I understand the inhibition of
16 phosphorylation have impact on both normal
17 cell and tumor cell because both of them have
18 wild-type EGFR expressed, but for you to draw
19 a conclusion that there's no change to ADC
20 therapeutic window, you have to assume the
21 change -- the impact on both normal cell and
22 tumor cell are to the same degree, correct?

1 MR. QIU: Objection, asked and
2 answered, and objection, unclear.

3 THE WITNESS: Yeah, I would say the
4 type of effect is the same.

5 BY MR. CHEN:

6 Q I'm not asking about the type; I'm
7 saying the degree of impact.

8 MR. QIU: Objection, unclear.

9 MR. CHEN: Which part is unclear?

10 THE WITNESS: But it's true, it is
11 unclear.

12 MR. QIU: The unclear -- "degree" is
13 unclear.

14 MR. CHEN: Well, the objection, if
15 you say "unclear," is vague, basically
16 vague, and based on the rule, you can
17 only object to the form. You cannot say
18 it in a speaking objection. You
19 specifically say like it's unclear.

20 MR. QIU: Counsel, so objection,
21 unclear, is actually what I learned from
22 Petitioner's counsel from last time.

1 MR. CHEN: I don't think so.

2 MR. QIU: Do you want to take off
3 the record and let's look at the
4 deposition transcript?

5 MR. CHEN: We're almost done here.

6 MR. QIU: Okay.

7 THE WITNESS: I would say it's
8 actually -- let me explain.

9 I think it's actually not that --
10 you know, a big issue really.

11 I think what we're doing is
12 comparing apples with oranges. How do
13 you measure an effect on tumor? How do
14 you measure an effect like toxicity?
15 These are two different measures.

16 BY MR. CHEN:

17 Q Yeah.

18 A Two different measures. And if
19 you're trying to compare an extent, you know,
20 what are you really doing?

21 Are you asking me to say, well, the
22 skin toxicity is going to be 20 times worse,

1 and the tumor is going to shrink 20 times
2 more. Is that comparable, or what's
3 comparable of the effect on the patient's
4 well-being or survival?

5 I think I'm just saying -- so to
6 assess toxicity and compare toxicity with
7 efficacy, and then to ask -- you know, you
8 need to like find the common variable for
9 both. I think that's -- it's not realistic I
10 don't think.

11 Q Not realistic to do that?

12 A I don't think that's -- not
13 possible.

14 Q Then if it's not realistic, how did
15 you draw the conclusion that says no change to
16 the ADC therapeutic window? That's my
17 question. How do you -- how did you draw that
18 conclusion then?

19 MR. QIU: Objection, asked and
20 answered.

21 THE WITNESS: Yeah.

22 Well, that's -- I was just going by

1 the effect -- you know, the same by the
2 biology and the effect and the
3 inhibition.

4 So I was assuming that the direction
5 of the effect, you know, will be the
6 same, will be similar, you know.

7 BY MR. CHEN:

8 Q Do you consider in a tumor cell,
9 based on Crombet, that 100-fold higher level
10 of EGFR than normal cell, how can that not
11 affect the degree of the impact?

12 A Because --

13 MR. QIU: Objection, argumentative.

14 THE WITNESS: How can it do that?

15 It does.

16 BY MR. CHEN:

17 Q No, my question is 100-fold.

18 A Yeah, I know.

19 Q EGFR.

20 A Yeah.

21 Q More than on the tumor cell relative
22 to normal cell.

1 A Yeah.

2 Q So when you are talking about the
3 impact on tumor cell and normal cell, did you
4 consider they are much higher copy of EGFR,
5 100-fold higher --

6 A Yeah, it's overexpressed.

7 Q -- than normal cell?

8 A Yeah.

9 Q Right, overexpressed, right?

10 A Overexpressed in tumor cells.

11 Q Right?

12 A Right, exactly.

13 But I can only repeat myself, but, I
14 mean, when comparing apples with oranges, and
15 I can tell you from my experience that,
16 you know, skin side effects, for example, can
17 be devastating and can ruin a person's quality
18 of life completely.

19 So you could say, well, it's just a
20 minor -- compared to the shrinkage in the
21 tumor, it's like a -- it's a relatively minor
22 comparable.

1 But if you take a different measure,
2 if you measure something else, quality of
3 life, for example, then the whole thing will
4 look different suddenly. You know what I
5 mean? So that's -- it's hard to say.

6 It's like, overall, I would say --
7 what I'm saying is it will increase both types
8 of cytotoxicity, against healthy and normal
9 cells, but -- you know.

10 And, yeah, I'm thinking that it's
11 possible that it won't affect, at least not to
12 a positive degree, the therapeutic window.
13 That's what I would think.

14 Q But you say that it's not realistic
15 to measure the impact, but it's more like
16 quantitatively you believe that, right? Does
17 not quantitatively, not realistic to measure
18 it, that's what you say, right?

19 A So, yeah, it's not easy to measure,
20 I think, but that's -- well, again, it's a
21 clinical question that one needs to define.

22 I mean, I don't want to go into -- I

1 could go into a long speech about like how do
2 you define a therapeutic window, but it's
3 not -- it's not that easy --

4 Q Mm-hmm.

5 A -- you know, but I'm sure -- and
6 I've said this -- but I think it's for
7 overexpressed antigens in general, if you
8 target them, and you effectively target them,
9 this will affect -- if you're lucky, it will
10 affect toxicity only -- if you're lucky, it
11 will affect both. If you're not that lucky,
12 it will just cause toxicity, and that's just
13 how it is.

14 Q So you talk about phosphorylation
15 here, right?

16 A Yeah.

17 Q So something for ADCC --

18 A I'm talking about one effect or
19 mechanism, yeah, on the mechanism of action.

20 Q So paragraph 64 you continue talking
21 about ADCC. So you follow same logic, right?
22 So you're saying --

1 A Yeah.

2 Q -- you're going to have parallel
3 change to both normal cell/tumor cell, and
4 that the impact -- correct me if I'm wrong --
5 the impact assumed to be the same degree?

6 A Yeah. So go in the same direction
7 or be similar.

8 Q Same direction?

9 A Yeah, same direction.

10 Q But it's not same degree. It's the
11 same direction, correct?

12 MR. QIU: Objection, unclear.

13 THE WITNESS: Yeah.

14 BY MR. CHEN:

15 Q Same direction?

16 A Same direction, and possibly --
17 well, yeah, that's all I can say. It will
18 have a similar effect.

19 Q You're not sure, may or may not be
20 the same degree?

21 A Exactly. That would be -- would
22 remain to be determined, right? I think it's

1 a -- I think -- well -- oh, my God.

2 Q That's okay. That's okay if
3 don't --

4 A I'm just saying, you know, if your
5 goal is to widen the therapeutic window, none
6 of these two would be approaches that I would
7 use, that's for sure. That's the more
8 important thing I think, you know.

9 Q So, Doctor, for ADC, right, there's
10 antibody, linker, and payload, so what's the
11 function of antibody?

12 A Oh, well, I mean, it has a multitude
13 of functions. Even for an ADC, it's not just
14 one, you know, function. We just talked about
15 two of the mechanisms.

16 Q Including phosphorylation?

17 A Including phosphorylation.

18 Q And ADCC?

19 A And ADCC, and mechanisms that --

20 Q What about tabulating, tabulating
21 the antigen on the tumor cell?

22 MR. QIU: Objection, form.

1 BY MR. CHEN:

2 Q That's a part of the function of
3 antibody, correct?

4 A Yeah, yeah.

5 Q So phosphorylation and ADCC you're
6 talking about here, they contribute to
7 inhibition or tumor growth, right?

8 MR. QIU: Objection, form.

9 THE WITNESS: I mean, so these
10 output -- well, let me just take these,
11 like inhibition of tumor growth, let me
12 take that out because that's a -- I mean,
13 that's a -- they both contribute to
14 antitumor effects.

15 BY MR. CHEN:

16 Q Okay. Efficacy?

17 A Antitumor effects, yeah.

18 Efficacy, again, it's a term that's
19 specifically used, you know, in a clinical
20 setting, you know, so ...

21 Q Okay. So I remember in your
22 declaration you were talking about cetuximab

1 even though it was approved like 20 years

2 ago --

3 A Mm-hmm.

4 Q -- but you don't see ADC using
5 cetuximab. Did I say that correctly, or I can
6 go to --

7 A Yeah, so you mean there is no ADC,
8 like no additional ADC that was approved?
9 That's what you mean?

10 Q Not approval, but we don't know
11 whether people use that cetuximab to create
12 ADC?

13 A ADC? Whether they use it?

14 Q Yeah.

15 A I mean, they've used --

16 MR. QIU: Objection, calls for
17 speculation.

18 THE WITNESS: Well, yeah. Well,
19 it's --

20 MR. CHEN: He's an expert, right? I
21 mean, I just asked whether he knows or
22 not.

1 MR. QIU: I don't think it's proper
2 for the expert to speculate in the
3 deposition setting.

4 MR. CHEN: Either he knows or he
5 doesn't know.

6 MR. QIU: So I have the right to
7 voice my objection. He will still answer
8 the question, right?

9 This is how it goes, right?

10 MR. CHEN: Fred, enough.

11 Answer if you are able.

12 THE WITNESS: Yeah. Are people
13 developing this? I mean, I would think
14 so, that people probably develop this,
15 but that's not my field really, so, you
16 know.

17 BY MR. CHEN:

18 Q Do you recall Wei reference that Wei
19 actually create a cetuximab with a vc-MMAE
20 ADC? Do you recall that?

21 A Yeah, yes.

22 Q So people did create

1 cetuximab-vc-MMAE ADC, correct? Okay.

2 So Cetuximab is a --

3 MR. QIU: Objection to the previous
4 question, mischaracterized the document
5 of Wei.

6 BY MR. CHEN:

7 Q So cetuximab is a chimeric antibody,
8 right?

9 A Yeah, I think so.

10 Q Okay. So do you think it's possible
11 that you don't see cetuximab-based ADC is
12 approved is because the cetuximab is not a
13 humanized version?

14 MR. QIU: Objection, calls for
15 speculation.

16 THE WITNESS: Yeah, I can't say what
17 the -- whether that's plausible. I think
18 it's possible, but anything is possible.

19 BY MR. CHEN:

20 Q Right, right.

21 A You know, so I don't know.

22 Q We don't know for sure?

1 A I can't say that, yeah.

2 Q We don't know for sure, right?

3 A Yeah.

4 Q Yeah. Could be a reason because we
5 don't know for sure?

6 A Yeah.

7 Q Correct?

8 A It's a -- it's a possibility, yeah.

9 Q Can I have a copy of the
10 Exhibit 2023.

11 MR. QIU: Doctor, would you like to
12 take a break?

13 THE WITNESS: Yeah, at some point.
14 I don't know how long the next spot is
15 going to take, but I need to go to the
16 bathroom.

17 MR. CHEN: Yeah, yeah, go ahead. We
18 can stop here, yeah.

19 THE WITNESS: Right now you think?

20 MR. CHEN: Yeah, yeah.

21 MR. QIU: Why don't we take a -- I
22 don't know --

1 MR. CHEN: 10 minutes?

2 MR. QIU: 10 minutes? Sure.

3 MR. CHEN: So we come back at 4:28,
4 27, 28, okay?

5 MR. QIU: Okay.

6 THE VIDEOGRAPHER: The time is
7 4:17 p.m. We are now off the record.

8 (A break was taken.)

9 THE VIDEOGRAPHER: The time is
10 4:30 p.m. We are now on the record.

11 BY MR. CHEN:

12 Q Doctor, welcome back. I would like
13 to give you a copy of the Exhibit 2023.

14 A Thank you.

15 Q You recognize this document, yeah?

16 A Yeah, Garrido.

17 Q Garrido, yeah. Where's my own copy
18 then?

19 You cited in your declaration about
20 bivalent binding, right, Garrido talking about
21 bivalent binding? So my understanding is
22 there's some antibodies, primarily monovalent

1 binding, right, some of them bivalent binding,
2 correct?

3 A Yes.

4 Q Cetuximab is a mainly monovalent
5 binding, correct?

6 A I think so.

7 Q So would you expect that the BA03
8 also mainly monovalent binding?

9 A Well, I'm not sure.

10 Q That's fine.

11 So what's an advantage of bivalent
12 binding?

13 MR. QIU: Objection, unclear.

14 BY MR. CHEN:

15 Q So let me rephrase if you don't
16 understand my question.

17 So this reference, 2023, is talking
18 about bivalent binding, right? So my question
19 is, compared to monovalent binding, what is
20 the advantage of bivalent binding for an
21 antibody?

22 MR. QIU: Objection, unclear.

1 THE WITNESS: Well, I think this --
2 the reason for why I used this was
3 primarily to provide one more explanation
4 for, you know, advantages or
5 disadvantages of low-affinity antibodies.
6 So I'm using the antibody that we've
7 talked about before, the nimotuzumab, as
8 an example.

9 So what I'm saying here is, and
10 that's explained in this -- in Figure 4,
11 is that, you know, with this -- with that
12 characteristic, low affinity of the
13 single antibody, in order to bind stably
14 to the EGFR, they typically would require
15 bivalent binding so that they have like
16 sufficient stability.

17 And what I'm using this reference
18 for is to say, as outlined in the
19 proposal, that these -- that this -- that
20 this -- like this type of binding, the
21 bivalent binding, is transient typically
22 on cells on which EGFR density is low,

1 and that that can reduce -- can lead to a
2 different or reduced toxicity in healthy
3 tissues that have a low -- low --
4 comparably low expression of EGFR.

5 BY MR. CHEN:

6 Q But that only applied to bivalent
7 binding antibody, right, such as the
8 nimotuzumab, correct?

9 A I would say it applies only to
10 bivalent antibodies. I mean, that's what we
11 talked about before.

12 Q Yeah.

13 A I mean, this does not only apply to
14 bivalent antibodies.

15 Q So I'm confused. Did you say they
16 apply only to bivalent antibody or not?

17 A I mean -- well, this exact
18 mechanism --

19 Q Yes.

20 A Obviously, I mean, it's in the
21 nature of bivalent antibody that it can only
22 apply to bivalent antibodies, right?

1 Q Okay.

2 A I mean, that's per definition in the
3 case, yeah.

4 Q Okay. So can you go to page 7 of
5 this reference?

6 A Yes.

7 Q I want you to take a look at the --
8 are you on the page 7 now? Okay.

9 A Oh, this says it's 8. Sorry, 7.

10 Q Page 7, okay.

11 A Yeah.

12 Q I want you to look at the last
13 paragraph -- last paragraph on the left.

14 A Mm-hmm.

15 Q It says that, "In summary, we have
16 provided elements to understand the dynamic
17 interaction of nimotuzumab with the receptor
18 in normal and tumor cells. Our findings
19 suggest that the intrinsic properties of
20 nimotuzumab require bivalent binding for
21 stable attachment, which leads to nimotuzumab
22 selectively binding to EGFR overexpressing

1 cells," right?

2 So my understanding is that the
3 bivalent binding contribute to the more
4 selectivity -- selective binding to tumor cell
5 for nimotuzumab. Is my understanding correct?

6 A I would -- yeah, I think I would
7 tend to agree that that's --

8 Q Okay. And then I will go on to read
9 the next sentence under -- actually, two more
10 sentences. So go like two or three lines
11 below that.

12 A Mm-hmm.

13 Q It says, "We propose bivalent
14 binding model as a refinement of the previous
15 'window affinity' hypothesis."

16 Do you see that?

17 A Yes.

18 Q Okay. So this reference actually is
19 talking about a refinement to the previous
20 model which is in the Crombet, right --

21 A Mm-hmm.

22 Q -- bivalent binding model.

1 So my understanding is it contribute
2 at least to some extent to bivalent binding,
3 not just the binding affinity, because Crombet
4 is talking about binding affinity, and this
5 reference kind of provide a refinement to that
6 saying that bivalent binding actually is the
7 main reason, correct?

8 MR. QIU: Objection,
9 mischaracterizes document.

10 THE WITNESS: Yeah, so I'm not sure
11 it's the main. It's saying it's a main
12 reason, that's all, but ...

13 BY MR. CHEN:

14 Q But it's an explanation provided
15 here?

16 A Yeah, it's one possible explanation.

17 Q Okay. I think I have the -- want to
18 talk about Wei reference. That's 1005.

19 I think that, Doctor, you have a copy of Wei
20 reference in your hand.

21 A Yeah, I think so.

22 Q Okay. Could you go to page 111?

1 A What does it look like?

2 Q Could you go to page 111, please?

3 A Yes.

4 Q Okay.

5 A Okay.

6 Q I want you to take a look at

7 Table 24. Table 24 is basically a binding at

8 pH 7.4?

9 MR. QIU: Which page?

10 MR. CHEN: Page 111.

11 MR. QIU: 111. Okay, got it.

12 BY MR. CHEN:

13 Q Okay?

14 A Yeah.

15 Q So the binding at pH 7.4 is not an

16 acidic environment, right? Tumor environment

17 is more acidic, whereas pH 7.4 is neutral?

18 A Neutral, yeah.

19 Q Almost neutral, right?

20 A Yeah.

21 Q And then on top of the first row, it

22 says Y104D, correct?

1 A On the very top --

2 Q Yeah, very top.

3 A -- in Table 24?

4 Q Yep, yep, yep.

5 A Yes.

6 Q And I want you to look at the --
7 because some of the -- some of the symbol I
8 try to understand myself. It's like D-h, E-h,
9 EP-h. And, in fact, you can look at the -- on
10 the left-hand side, paragraph 1004.

11 A Mm-hmm.

12 Q He actually explain that, right? So
13 basically the humanized Y104D, abbreviation is
14 D-h, correct? Do you see that?

15 A D-h.

16 Q Right. D-h is humanized Y104D,
17 correct?

18 A Mm-hmm.

19 Q And then E-h is humanized Y104E,
20 correct?

21 A Mm-hmm.

22 Q And then the EP-h is humanized --

1 basically have double mutation, right? It's
2 Y104D and Q111P.

3 Actually, if we look at this same
4 paragraph, if you look, you know, a little bit
5 further down, like the last two or three
6 lines, it actually says that type of mutation
7 there, D and B, okay?

8 A Mm-hmm.

9 Q And then if you compare the binding
10 to the EGFR at the pH 7.4, this is an ELISA
11 assay, right?

12 A Mm-hmm.

13 Q So, Doctor, can you -- if you look
14 at, for example, the top row again, the Y104D,
15 this is not a humanized version, the EC50, how
16 much is that?

17 A So we're talking about Table 24
18 again?

19 Q Table 24, yeah.

20 A For Y104D?

21 Q Yeah, column C. Column C.

22 A Yeah, that's 8.33.

1 Q 8.33, right.

2 And then you look at the D-H.

3 D-h is how much? 30.2, is that

4 right?

5 A So D-h, 30.2 I think.

6 Q Right, 30.2.

7 And then E-h is 46.1, right?

8 A Gees.

9 Q Small. Yeah, small form, right.

10 A It's in the same column?

11 Q Same column. It's column C, EC50,

12 right?

13 A Yeah, right. And we're talking

14 about E-h, correct?

15 Q E-h.

16 A EP-h.

17 Q E-h, E-h for now, is 46.1, correct?

18 A Yeah.

19 Q So EC50, right, higher EC50 value

20 means weaker binding, right?

21 A Yes.

22 Q Okay. So this humanized version is

1 a D-h/E-h, compared to the unhumanized
2 version, Y104D on the top, the binding
3 actually is weaker, correct, because the
4 EC50 is higher now compared to 8.33?

5 Do you see that?

6 A Yeah. Well, yeah, I would think so.

7 Q Okay. So basically the humanized
8 version actually has a higher EC50 compared to
9 unhumanized version, which translate into
10 weaker binding, right?

11 A Can you repeat that again?

12 Q So I'm just kind of reiterating what
13 we say earlier. It's basically for D-h, E-h,
14 right, the EC50, 30.2 and 46.1, is higher than
15 8.33, right?

16 A Yeah, that's correct.

17 Q So this translate to weaker binding?

18 A Yeah.

19 Q Okay.

20 A I have a question.

21 Q Mm-hmm.

22 A Does this -- let me -- like I need

1 to take a look at the respective paragraph
2 because I'm wondering what is R2? That's the
3 effect -- that's the -- what is it?

4 Q R2 are the statistics, right?

5 A Yeah, I know, but --

6 Q Is that -- yeah.

7 A Yeah, I know, that's why I'm
8 wondering. That's why I'm wondering is this
9 like -- does this mean it's not significant?

10 Q It's two double digit, .99.

11 A Yeah, but that's --

12 Q Pretty good.

13 A No, I'm not sure. I'm not sure
14 really. I mean, there's no legend to this, so
15 I'm having doubts really on whether -- where
16 does it say what this is?

17 Also, what's the correlation? Where
18 does it talk about the Table 24?

19 Q That's example paragraph, 1003 to
20 1005, that basically reference Table 24.

21 1005, the assay, ELISA assay, the
22 binding of the His-tagged, 1004,

1 paragraph 1004, the paragraph above, it
2 basically used the EGFR, right, the
3 extracellular domain of EGFR in His-tagged
4 version to do the measurement using the
5 ELISA -- you know, using the different pH,
6 pH 7.4, 6.5, 6.0, I think there's the three
7 tables there, right? Table 24, 25, 26.

8 In 24, we were just looking at this
9 pH 7.4, and the reported, you know, different
10 EC50 value for unhumanized version, and then
11 humanized version have D-h, E-h, EP-h, or the
12 humanized version.

13 A Yeah, yeah.

14 Q Right? So I guess, you know, let's
15 look at the EC50 value, and we do see that for
16 D-h, the EC50 is a 30.2, right? And then E-h
17 is 46.1, EP-h, 69.8, and for the unhumanized
18 version on the top is 8.33, right?

19 A Yeah.

20 Q That's what we see, right?

21 A Yeah.

22 Q I think -- you know, basically I

1 want to just get a confirmation that you do
2 understand higher EC50 value means the weaker
3 binding?

4 A Yes.

5 Q You agree with that, right? Okay.

6 What else? Anything?

7 So, Doctor, in general, like
8 cetuximab, you mentioned that cetuximab has
9 pretty stronger binding affinity to EGFR,
10 wild-type EGFR, correct?

11 A Stronger?

12 Q Strong compared -- I guess compared
13 to nimotuzumab, has a stronger binding
14 affinity to EGFR?

15 A Yeah, I think -- I would think so,
16 yeah, it has a low affinity.

17 Q So correct me if I'm wrong. It's
18 your opinion, you know, you say that cetuximab
19 may not be ideal, may not be the best
20 candidate for the ADC, right?

21 A Mm-hmm.

22 Q But nowhere in any reference you

1 cite, nowhere in any reference says, hey, you
2 should not use cetuximab for ADC, correct?

3 MR. QIU: Objection, form.

4 THE WITNESS: Well, I don't think
5 this -- like the way you put this
6 question, I would think it's possible
7 that it's not, but it's saying some --
8 like -- and we've gone through all this
9 before, that an antibody like cetuximab,
10 you shouldn't -- it's not the best idea
11 to use that, right.

12 BY MR. CHEN:

13 Q Yeah.

14 A So that's what we've said before.

15 Q I think that's your opinion, not the
16 best, not ideal, but I'm trying to understand,
17 you are not saying that a POSA would
18 understand there's a -- you know, I just want
19 to -- I don't want to use cetuximab at all
20 because it's a -- I guess put it differently,
21 stronger binding affinity is not a barrier,
22 right? It's not a -- you know, there's no

1 category of barrier saying that don't never
2 use high-binding affinity antibody for ADC,
3 right? That's my question.

4 MR. QIU: Objection, form.

5 THE WITNESS: Well, I don't think
6 that that's how a POSA would think, in my
7 opinion. I don't think they would say --
8 think that way, but they would try to
9 determine what's the -- like what
10 characteristics to avoid and what
11 characteristics to prefer.

12 BY MR. CHEN:

13 Q Right.

14 A And if they go by all the different
15 characteristics, they would have said, in my
16 opinion, and we've talked about all this
17 before, they would say -- probably say, in
18 order to avoid toxicity or enhanced toxicity
19 or significant toxicity, I would prefer
20 lower-affinity antibody over high affinity.

21 BY MR. CHEN:

22 Q Okay, I see. Okay, got you. It's

1 more of like preference.

2 Again, it's basically saying your
3 opinion is that cetuximab may not be ideal or
4 the best candidate for ADC?

5 MR. QIU: Objection, asked and
6 answered.

7 BY MR. CHEN:

8 Q Correct?

9 A So that's definitely the case, but I
10 would go farther and say -- well, if they have
11 toxicity in mind, they will try to avoid, you
12 know, a higher affinity antibody, in my
13 opinion.

14 Q But you agree that this is a
15 balancing act, right? You have to balance
16 between efficacy and toxicity, right? You
17 balance these two factors, correct?

18 A That's -- well, that's not what I
19 do, but that's I think -- yeah, you want to
20 keep the therapeutic window in mind. That's,
21 by definition, a balance.

22 Q Okay.

1 A You know.

2 Q But you talk about therapeutic
3 window a lot in your declaration.

4 A Yes.

5 Q So in order to have a reasonable
6 therapeutic window, you do need to balance
7 between efficacy and toxicity, right?

8 A Yeah, you need to find some,
9 you know, way to take both factors into
10 account, you know.

11 Q Mm-hmm. Let's take a 10-minute
12 break. I need to go through my notes and see
13 whether I have any residual questions to go
14 through. If not, then we call it a day,
15 all right?

16 A All right.

17 Q Thank you.

18 MR. QIU: All right.

19 THE VIDEOGRAPHER: The time is
20 4:55 p.m. We are now off the record.

21 (A break was taken.)

22 THE VIDEOGRAPHER: The time is

1 5:06 p.m. We are now on the record.

2 BY MR. CHEN:

3 Q Doctor, in your CV, you record that
4 you list almost 150 papers.

5 A Mm-hmm.

6 Q How many papers that directly relate
7 to ADC?

8 A That directly relate to ADC? I
9 don't remember really. It's -- oh, I don't
10 remember.

11 Q Okay.

12 A I think -- well, I have to go
13 because it's such a long -- it's such a long
14 list of, you know, publications, I don't -- I
15 don't remember.

16 Q Okay. Do you know like -- let me
17 see. You can look at your declaration.

18 A Oh, yeah.

19 Q I think there's an appendix
20 somewhere. Can you quickly skim through that,
21 let me know like which paper directly relate
22 to ADC.

1 A I think -- I would say that depends
2 on how you look at it. I mean, if you talk
3 about ADC, you talk about antibodies as well,
4 right, and the quality of an antibody and all
5 these things. So I would personally -- I
6 think any paper on an antibody is related, is
7 directly -- is at the same time related to ADC
8 as well -- to ADC as well.

9 For example, all the papers that we
10 have on the CD229 target, that's a patent that
11 we have, an issued U.S. Patent, and that's for
12 the monoclonal antibody ADC, and even
13 CAR T-cells, so that's -- they're all part of
14 the claim.

15 And as part of this project,
16 for example, which represents I think a large
17 part of the publication, you know, so ADC is
18 part of this. So we've developed our own
19 antibody.

20 Well, I would consider,
21 for example -- that's an example. I could
22 consider this, all the complete CD229 work, I

1 would consider it as direct relevance to ADC
2 as well.

3 And I can talk more about this. So
4 I've done a lot of work on antibodies and
5 antibody modification and these kind of
6 things, so ...

7 Q Did you ever create an ADC?

8 A Yeah, we've created an ADC.

9 Q On which antibody?

10 A So that's in our own antibody that
11 we've used a 2D3 clone against. It's one of
12 the clones that we've generated against CD299.

13 Q What kind of payload did you use?

14 A I think it was MMAE or something. I
15 don't remember exactly. It was at the
16 University of Utah, and it wasn't very
17 successful, I'll have to say, so ...

18 But, you know, there are other
19 targets that we have used where we've
20 developed a different, so I could -- you know,
21 that's actually one of our main fields of
22 activity these days is to generate antibodies

1 against different targets and use them for
2 different types of immunotherapies and --
3 yeah.

4 And, you know, if you want to look
5 at, for example, cetuximab, I would say it has
6 relevance to at least one ADC. I mean, I have
7 clinical -- led clinical trials with that
8 antibody as well. So it's a mixture of, say,
9 preclinical work and clinical work.

10 Q Is that clinical trial you mentioned
11 on page 61 of your declaration?

12 A That's the lung cancer, I think.

13 Q Yeah, it's NSCLC, right?

14 THE REPORTER: What's the number?

15 MR. CHEN: This is still on
16 declaration, 2027, page 61.

17 BY MR. CHEN:

18 Q So, Doctor, I just want to be sure.
19 Are you referring to a clinical trial called
20 CERTO, C-E-R-T-0? That's on page 61.

21 A Yeah.

22 Q 61.

1 A 61.

2 Q Yeah.

3 A Yeah, sorry.

4 Q The page number is on the bottom

5 right.

6 A Oh, gosh.

7 Q Yeah, look at the right-hand side,

8 bottom.

9 A Oh, that's the clinical trials.

10 Yeah, I think that was one of the

11 trials. Yeah, I think so.

12 Q Okay, let's stay on that one. I
13 want to ask you, so the CERTO, C-E-R-T-O, is
14 an open-label, randomized, controlled,
15 multicenter Phase II study investigating --
16 how do you say this?

17 A Cilengitide.

18 Q Cilengitide in combination with
19 cetuximab and platinum-based chemotherapy,
20 then I want to skip that, compared to
21 cetuximab and platinum-based chemotherapy
22 alone, right, as a first-line treatment for

1 patients with advanced NSCLC, right, CERTO?

2 A Mm-hmm.

3 Q So this is a Phase II, right?

4 A Mm-hmm.

5 Q Already did a Phase I?

6 A So someone did the Phase I, yeah.

7 Q You already did Phase I?

8 A Yeah.

9 Q So Phase I is safety?

10 A Phase 1, yeah, is safety.

11 Q So studied the safety. So you
12 passed the Phase I, then you're going to --
13 then you're going into Phase II, correct?

14 A Yes, right. That's typically how it
15 goes, yeah.

16 Q And then the therapy you investigate
17 here is a combination therapy of the cetuximab
18 plus cilengitide, compared to cetuximab alone,
19 and then a platinum-based chemotherapy.

20 Okay, actually, the combination is a
21 threefold combination. It's threefold, right?
22 Cetuximab, cilengitide, plus a platinum-based

1 chemotherapy, right? And then you compare to
2 platinum-based chemotherapy alone and the
3 cetuximab alone.

4 So that combination therapy already
5 passed Phase I, right? So it's safe, so
6 that's why you enter into Phase II?

7 A Yeah, the question for Phase II is
8 twofold. It's still safety. Safety is going
9 to be your like primary goal still, you know.

10 And then you'll start to assess some
11 early signs of clinical activity in the sense,
12 you know, that you measure efficacy, you know,
13 but the primary goal will still be safety.

14 Q But safety out of Phase I at least
15 means that it is acceptable to move into
16 Phase II, correct?

17 A Yeah, I think most of the times
18 that's probably how it is.

19 Q So you used the cetuximab here. How
20 did you manage the toxicity of the cetuximab?

21 A Well, that was a relatively long
22 time ago, I mean 15 years ago, but I think

1 they managed -- so, yeah, I remember for all
2 these trials, not just for the trials --
3 there's another trial, by the way, that's the
4 POSEIDON trial, that used the same antibody in
5 colorectal cancer, and for all these we had
6 significant toxicity.

7 So like are you asking how did we
8 manage this in an individual in a patient?

9 Q Yeah.

10 A Yeah, I mean, it depends really on,
11 you know, what type of toxicity. If it's skin
12 toxicity, I mean, you can do -- it depends on
13 the severity of the -- on the grading of the
14 toxicity.

15 You know, if it's mild, you can do
16 this and that, use topical agents like creams
17 and these kinds of things.

18 If it's more extensive, you'll have
19 to use even antibody -- I'm sorry,
20 antibiotics.

21 Q Antibiotics?

22 A Antibiotics, you know, to treat

1 them. And, you know, yeah, it depends really.

2 Q How can the antibiotics actually
3 treat skin, you know, rash toxicity?

4 A That's a great question. I'm not a
5 dermatologist, I mean, but -- well, if it's
6 inflamed, if there's an infectious component,
7 a skin bacteria, you know, then you use
8 antibodies -- antibiotics.

9 Q So this one is -- sorry.

10 So this one is the advanced --
11 NSCLC, right, advanced lung cancer.

12 A Mm-hmm.

13 Q It's pretty deadly, right?

14 A Yes.

15 Q Pretty deadly?

16 A Mm-hmm.

17 Q So you do think that the efficacy is
18 very important to cure the patient, right,
19 because they are so deadly?

20 A Well, we're when mixing a lot of
21 things now. Well, I've never said efficacy is
22 not important. That's something that I've

1 never said. So I think, yes, that plays a
2 role, obviously, for clinical trials, where I
3 do think that even at this stage, and
4 obviously for earlier stages, and just in
5 general for every patient, I think safety
6 should always come first.

7 So when I sit down with a patient,
8 first thing I do is I go over side effects,
9 and then I go over what they can expect from
10 the treatment, you know, so ...

11 Q But if you have a terminal disease
12 like that, do you also care about efficacy at
13 all? You have a skin rash, right, but I
14 really want to be cured because this is an
15 advanced stage of terminal disease.

16 A You always take all of these --
17 that's why I'm saying. I mean, you need to
18 define a balance, right? That's what you do,
19 not just for studies, but for every individual
20 as well. You sit down with them, and then
21 you'll try to find a balance, but I can't
22 exaggerate like the -- you know, the

1 importance of side effects.

2 For you, it's maybe just a skin
3 rash, but for these people, it can be
4 devastating if they have like skin rashes all
5 over the place. It can ruin them, I mean ruin
6 their quality of life really, you know.

7 If it's something else, if it's GI
8 symptoms, this can like bring you to your
9 knees these side effects.

10 So I think that's -- one shouldn't,
11 you know, ignore this. It's very important as
12 well, that's all.

13 Q Right, I agree that safety is very
14 important. I think, you know, it is fair to
15 say you have to balance both efficacy and
16 safety, correct?

17 A Yeah, that's what I'm saying.

18 Q Let me go through -- so, Doctor, you
19 heard about HER2, right? HER2, H-E-R-2.

20 A Yes. The antigen?

21 Q Are you aware that HER2 also express
22 on tumor cell and normal tissue?

1 MR. QIU: Objection, relevance.

2 THE WITNESS: So, yeah, I'm not --
3 well, HER2 is not my field of expertise
4 really, but I don't feel confident making
5 any like definitive statements on that,
6 you know.

7 BY MR. CHEN:

8 Q Okay. Can I get Exhibit 1010?

9 So, Doctor, this Exhibit 1010 was
10 cited in, you know, Petitioner's petition
11 previously, and I want you to go specifically
12 to page 10.

13 Okay, so there's a subheading there,
14 right, number 4, "Antibody: The Precision
15 Guide in ADC Therapy," right?

16 You see that, right?

17 And then it go on and says, "The
18 antibody moiety of the ADC serves as the
19 tumor-targeting vehicle. As such, it should
20 display high Ag specificity, strong binding
21 affinity, and efficient cellular uptake."

22 Do you see that?

1 A Mm-hmm.

2 Q So do you understand what does it
3 mean, "efficient cellular uptake"?

4 A Yes.

5 Q What does that mean?

6 A I mean, if it's an ADC, it talks
7 about, you know, uptake of the antibody and
8 cytotoxic agent, yeah.

9 Q Does that include like
10 internalization?

11 A Internalization. By
12 internalization, yeah.

13 Q So here it says that the antibody
14 should have a strong binding affinity, right?
15 Do you see that?

16 A I see that. I can see that.

17 Q Do you agree with that?

18 A No.

19 Q You don't agree, that's fine.

20 A No, I don't agree with that.

21 Q Okay. Can I have a copy of 1019?

22 Okay, so Counsel.

1 MR. QIU: Thank you.

2 BY MR. CHEN:

3 Q So this is Exhibit 1019. It's also
4 a reference that's cited in the petition,
5 right?

6 I want you to go to page 5. This
7 time the page number is on the top of the
8 page. Page 5, do you see that, Doctor, page 5
9 on top of the page?

10 A Mm-hmm.

11 Q Okay. I want you to take a look at
12 the left-hand side, and then there's a
13 paragraph starting with "Antigen
14 internalization." Do you see that?

15 A Yes, I think so.

16 Q Okay, I will read.

17 "Ideally, once an ADC binds to a
18 tumor-associated target, the ADC-antigen
19 complex is internalized in a rapid and
20 efficient manner. Although poorly understood,
21 various factors are likely to influence the
22 rate of internalization, such as the epitope

1 on the chosen target antigen bound by the ADC,
2 the affinity of the ADC-antigen interaction
3 and the intracellular trafficking pattern of
4 the ADC complex."

5 So, Doctor, what it says here is
6 that the factor that affect the rate of
7 internalization would include an affinity of
8 the binding, right, of the ADC to antigen
9 injection, correct?

10 A That's what it's saying.

11 Q That's what it says, right?

12 Correct me if I'm wrong. Earlier
13 you testified that stronger binding, in
14 principle, can result in higher degree of
15 internalization of ADC, correct?

16 A That's possible, yeah.

17 Q Okay. So what's intracellular
18 trafficking?

19 A I would say that's -- well,
20 intracellular -- I mean, it's hard to say
21 because I would have to, I mean, assume what
22 they're saying.

1 I could imagine that they're talking
2 about lysosomes maybe, like trafficking within
3 lysosomes, but without any additional
4 information, it's hard for me to say,
5 you know. That's possible --

6 Q Mm-hmm.

7 A -- that it's --

8 Q You can put that aside, please.

9 So, Doctor, you have been deposed
10 before, right?

11 A Mm-hmm.

12 Q Did you serve as a fact witness or
13 expert witness?

14 A Yes.

15 Q Expert witness, right?

16 A I've served before as an expert
17 witness, yeah.

18 Q Can you tell me what kind of case is
19 that?

20 A The one where I was deposed?

21 Q Yeah.

22 A That was a case -- I can talk about

1 that, right?

2 Q Only public information.

3 MR. QIU: Yeah, just -- yeah.

4 MR. CHEN: Do not disclose any
5 privileged information. I want you to
6 only talk about publicly available
7 information.

8 THE WITNESS: Okay.

9 Well, that was a case that was about
10 cancer treatment as well for, you know, a
11 certain type of malignancy, and was a
12 patent litigation case.

13 BY MR. CHEN:

14 Q In a court, right? District court?

15 A I think, yes, yeah, and that was
16 where I served for the -- I think, yeah, the
17 Patent Owner, and I provided my opinion on
18 the -- on the -- on this drug -- on this drug
19 and the patent, yeah.

20 Q Mm-hmm. Does that relate to
21 antibody or relate to ADC?

22 A No, that one was not related to

1 either one.

2 Q Okay.

3 A It was a different type of --

4 Q Drug.

5 A Drug, yeah.

6 Q Have you ever served as an expert
7 witness for any antibody or ADC related drugs?

8 A Mm-hmm.

9 Q Such as? Can you give me examples?

10 A Yeah. I've served -- oh, my gosh.
11 I've served as an expert -- do I have to
12 provide all this information? I'm just not
13 sure what's appropriate.

14 MR. QIU: Yeah, I think, yeah, just
15 state --

16 THE WITNESS: I don't know what's
17 public, that's the thing. I have no
18 idea. I don't know like what part of
19 this --

20 BY MR. CHEN:

21 Q I don't want to know the detail. I
22 don't even want to know like molecule's name.

1 Just general, something general.

2 A Okay. So, yeah, I've served for,
3 again, a patent litigation case that was
4 related to lymphoma and an antibody treatment
5 for lymphoma.

6 I've also served as an expert
7 witness for a case that was related to -- it
8 was actually two different cases that had
9 something to do with an antibody and the use
10 of this antibody for different -- different
11 purposes, including ADC, and also CAR T-cells
12 at the time, so -- and, yeah, that was also a
13 patent litigation case for a blood cancer, a
14 type of blood cancer.

15 Q So for all cases, did you retained
16 by -- were you retained by the patent owners?

17 Let me put it differently.

18 Have you ever been retained by
19 Petitioner --

20 A Yes.

21 Q -- or the challenger --

22 A Yes.

1 Q -- or accused infringer?

2 A Yes.

3 Q Yes?

4 A Yes.

5 Q Okay. So have you ever worked with

6 the Patent Owner in this case before, like

7 LEPU --

8 A No.

9 Q -- or Miracogen? No?

10 A Not to my knowledge at all.

11 Q In the previous cases you mentioned,

12 have you worked with the counsel in this case?

13 A No.

14 Q No? It was a different counsel,

15 different law firm?

16 A Yeah.

17 Q Okay. So you mentioned in your

18 declaration that you were paid compensation.

19 A Mm-hmm.

20 Q It's a standard rate.

21 A Mm-hmm.

22 Q What's that number?

1 A That's \$800.

2 Q Per hour?

3 A Per hour, yeah.

4 MR. CHEN: How much time left?

5 Sorry.

6 THE VIDEOGRAPHER: 14.

7 MR. CHEN: Sorry.

8 THE WITNESS: That's fine.

9 BY MR. CHEN:

10 Q I don't want to ask you to come
11 back, that's why I try to cover at least most
12 of my questions, you know, so apologize for
13 that. I tried to let you go early.

14 I did travel to D.C. for this
15 deposition twice.

16 A I know, sorry.

17 Q No problem. I understand.

18 So finally about dosing.

19 Say cetuximab, and then if people
20 make a cetuximab-based antibody, ADC, right,
21 ADC, would the ADC usually use -- is used at
22 the lower dose than naked antibody, or same

1 level, or higher level? Do you know?

2 MR. QIU: Objection, incomplete
3 hypothetical.

4 BY MR. CHEN:

5 Q Answer to the extent you are able,
6 yeah.

7 A Well, I'm not sure. I don't know,
8 yeah.

9 Q Okay, that's fine. That's fine.
10 So earlier we talk about bystander
11 effect, right?

12 A Mm-hmm.

13 Q So did you mention even like
14 bystander effect in your declaration? Do you
15 remember?

16 A I don't -- I'm not sure I used the
17 term, actually, yeah.

18 Q Is there any alternative term you
19 use to the bystander effect?

20 A Well, I think I talk about -- I know
21 I talk about the tumor microenvironment and
22 the immediate environment of the tumor, so

1 that would include bystander -- I think would
2 include bystander -- the bystander effect as
3 well, yeah.

4 Q Mm-hmm. Doctor, thank you so much.
5 We appreciate your time, and I think we have
6 all the questions asked, yeah.

7 A Okay, great. Thank you so much.

8 MR. QIU: Patent Owner has no
9 redirect.

10 MR. CHEN: Okay.

11 THE VIDEOGRAPHER: Counsel, does
12 this conclude for today's deposition?

13 MR. QIU: Yes.

14 THE VIDEOGRAPHER: Okay, this
15 concludes for today's deposition. The
16 date is April 14, 2026. The time is
17 5:37 p.m. We are now off the record.

18 (Whereupon, at 5:37 p.m., the taking
19 of the deposition was concluded.

20 Reading and signature were

21 RESERVED.)

22

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 _____
4 CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,
5 Petitioner,
6 v.
7 SHANGHAI MIRACOGEN INC.,
8 Patent Owner.

9 _____
10 Case No. IPR2025-00685
11 U. S. Patent No. 10,792,370

12 ACKNOWLEDGMENT OF DEPONENT

13 I, DJORDJE ATANACKOVIC, M.D., do hereby
14 acknowledge that I have read and examined pages 1
15 through 359, of the transcript of my deposition
16 taken on Tuesday, April 14, 2026, and that:

17 (Check appropriate box):

18 () the same is a true, correct and complete
19 transcription of the answers given by me to the
20 questions therein recorded.

21 () Except for the changes noted in the attached
22 errata sheet, the same is a true, correct and
complete transcription of the answers given by
me to the questions therein recorded.

DATE SIGNATURE

1 WITNESS: Djordje Atanackovic, M.D.

2 DATE: April 14, 2026

3 CASE NAME: CSPC Megalith Biopharmaceutical v.
4 Shanghai Miracogen

5 CASE NO. : IPR2025-00685

6 Please note any errors and the
7 corrections thereof on this errata sheet. The
8 rules require a reason for any change or
9 correction. Reason Codes:

10

11 1. To clarify the record.

12 2. To conform to the facts.

13 3. To correct transcription errors.

14

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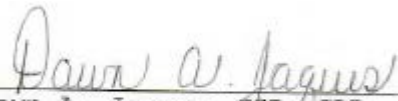
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CERTIFICATE OF NOTARY PUBLIC

I, DAWN A. JAQUES, a Notary Public in and for the District of Columbia, before whom the foregoing deposition was taken, do hereby certify that witness whose testimony appears in the foregoing pages was duly sworn by me; that the testimony of said witness was taken by me in shorthand at the time and place mentioned in the caption hereof and thereafter reduced to typewriting under my supervision; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition is taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties thereto, nor financially or otherwise interested in the outcome of the actions.


Dawn A. Jaques, CSR, CLR
Notary Public in and for
District of Columbia

My commission expires:
February 28, 2030