

1 | care of the wounds in some manner. And there's really no
2 | good way to control that that I know of, other than just
3 | the local wound care that we're offering those patients.

4 | Following treatment with IntraDose, there is a
5 | very predictable pattern to the wound healing process. The
6 | eschar forms first. The necrosis comes next, and then the
7 | re-epithelialization comes third. It's fairly typical and
8 | standard, and it doesn't differ from patient to patient. I
9 | think that it's easy to take care of those wounds and you
10 | really don't have to worry about the depth of your
11 | injection causing the effect at the deepest recesses of the
12 | wound because it generally happens in a very superficial
13 | manner that all this occurs. So, potential damage to the
14 | carotid, which you would think would happen from deep wound
15 | necrosis, for lack of another term, really doesn't happen
16 | so much.

17 | DR. NERENSTONE: Dr. Couch.

18 | DR. COUCH: What defines close proximity? The
19 | answer of a plane -- is there going to be more of a
20 | definition than that for what constitutes a patient that is
21 | appropriate for this therapy?

22 | DR. ELIAS: Well, I think we can clearly
23 | contraindicate the dangerous situations based upon our
24 | large experience in this disease in this phase III trial.
25 | Recall, when the amendment was instituted, directions were

1 given to the physicians and these directions were
2 remarkably effective at reducing the incidence of related
3 events and the subsequent part of the trial, which was more
4 than half the trial.

5 Specifically, the occurrence of these events
6 were reduced to 0 zero in more than 100 patients, and this
7 is unlikely to have happened by chance alone. So, we would
8 use in our indication wording very similar, if not
9 identical, to the amendment wording, which clearly was
10 meaningful to the physicians and useful guidance, and could
11 be interpreted by physicians, as Dr. Mills indicated.

12 DR. COUCH: I don't mean to beat this, but it's
13 such an important point. One last question. So, once you
14 made the amendment, patients that had cervical disease, the
15 same percentage was treated. In other words, what types of
16 patients were then excluded by these physicians so that
17 they did not have complications?

18 DR. ELIAS: The amendment excluded patients who
19 had tumors directly involving or adjacent to the carotid
20 artery.

21 DR. COUCH: So, a decrease in the percentage of
22 patients with cervical disease was then treated in the
23 protocol after that?

24 DR. ELIAS: I don't know if the percentage of
25 patients with cervical disease changed after the amendment.

1 The amendment also excluded patients with larger tumors,
2 and we would continue to not recommend treating larger
3 tumors, tumors greater than 20 centimeters cubed in the
4 head and neck region.

5 DR. HOWELL: You are correct. There was a
6 slight decrease in the absolute number of cervical
7 patients, appropriately so. Once you take that subset of
8 patients out, there are going to be fewer cervical
9 patients.

10 DR. RUBENSTEIN: We understand that patient
11 benefit was made a co-primary endpoint in mid-trial, and it
12 also appears that it was defined as a single endpoint in
13 mid-trial too, that up to that point there were multiple
14 endpoints and they were defined as a single one in mid-
15 trial.

16 What other aspects of patient benefit were
17 defined in mid-trial? Was the 28-day requirement
18 introduced in mid-trial? Was the 1-point scale difference
19 introduced in mid-trial?

20 DR. HOWELL: I apologize for being unclear.
21 There was initially one single primary endpoint. There
22 weren't multiple endpoints that were collapsed together in
23 some way. In an attempt to find a way of quantitating
24 clinical benefit, and working with the FDA, struggling with
25 this, we tried to come up with the patient benefit

1 algorithm, and eventually the FDA asked us to analyze that
2 as a co-primary endpoint in the trial. Dr. Morgan can
3 certainly speak to that in more detail if you care to.

4 DR. RUBENSTEIN: No, no. So, the endpoint
5 itself was defined from the beginning. It's just that it
6 became a co-primary endpoint in mid-trial.

7 DR. HOWELL: That is correct.

8 DR. NERENSTONE: Dr. Lippman.

9 DR. LIPPMAN: Just to follow up on the
10 amendment and the toxicity issue that was discussed in
11 terms of cerebrovascular events. Excluding stratum 3,
12 greater than 20 centimeter tumors, I had the impression
13 from the briefing document on page 31, that it was done
14 because of a low response rate. Was it done because of a
15 low response rate, or concern about increased toxicity, or
16 both?

17 DR. HOWELL: Was the dose reduced because of a
18 low response rate?

19 DR. LIPPMAN: Well, no. There were several
20 amendments made at the same time, I guess.

21 DR. HOWELL: Right.

22 DR. LIPPMAN: The question raised here about
23 the concern about proximity of the carotid and so on, that
24 in response to that answer, and why you're not as concerned
25 that this major side effect would occur with the new

1 dosing, I had the impression that the main issue there was
2 that the dose was reduced. But as part of the last answer,
3 there was a comment also that the stratum 3 patients were
4 reduced.

5 So, the question I have is, what was the basis
6 for removing the stratum 3 patients? Was it based on low
7 response rate, or increased toxicity, or both? And I'd
8 also, if you have it, I'd like to see the data on those
9 patients' response to toxicity.

10 DR. HOWELL: Sure. I think there are several
11 parts to that question.

12 One is -- and I'll ask Dr. Leavitt to address
13 it. One is there were two changes that were made
14 simultaneously in amendment five. One was a change in
15 patient eligibility that excluded the patients with carotid
16 tumor involvement, no matter what the size of the tumor
17 was. And the second was the change in the recommended
18 dose. And the change in the recommended dose came about
19 simply based on the experience in head and neck tumors,
20 where it was discovered that on the average they just
21 weren't accommodating quite as much gel as many of the
22 other types of tumors that have been studied.

23 DR. LIPPMAN: Wasn't there a third major aspect
24 to that, and that's excluding the large tumors? I thought
25 there were three major changes.

1 DR. HOWELL: Yes, you're right. That was a
2 third element in the amendment. Let me let Dr. Leavitt
3 address that.

4 DR. LEAVITT: Specifically at that point in the
5 trial, we examined all the data on all of the patients. We
6 looked at the patients in stratum 3 and removed them from
7 further entry in the trial because in advanced relapse
8 cancer, it was clear at that time that stratum 3 patients
9 had both a lower response rate and less opportunity to
10 benefit. And because of that, that was the reason that
11 they were removed from trial.

12 We looked at the response rate in stratum 3,
13 and overall this was a 13 percent response rate and because
14 of that we simply felt that this was too low a response
15 rate to justify any increased toxicity in this group. When
16 you also look at the benefit rate, which I'm not showing
17 you -- well, let me do that.

18 Now focus just on stratum 3, looking at the
19 benefit rate. This is also lower. It was 16 percent. And
20 given the low response rate, the lower benefit rate, it
21 seemed that it was not wise to keep these patients in
22 trial.

23 I'll also add that this study was designed
24 initially only for patients that we call stratum 1 and 2,
25 and it was at the insistence of investigators that they

1 also had an additional group of patients for whom they
2 essentially didn't have good alternatives for therapy.
3 They felt that it was important to explore whether this new
4 therapy might be an important breakthrough for such
5 patients. I hope in the future we can find a way to deal
6 with patients who have such large tumors, perhaps further
7 studies that look at the different treatment paradigms
8 using IntraDose, either alone or with other therapies,
9 might bring some benefit to these patients.

10 DR. LIPPMAN: The reason that I'm focusing on
11 this group for one is that, as you know, this is going to
12 be the most tempting group to treat, and that's I think why
13 the investigators asked for you to open it up to that
14 group. And I think when you talk about how these tumors
15 are measured, I don't know that precisely we can
16 distinguish 19 centimeters from 21. So, patients will be
17 treated with these big tumors for both reasons. They have
18 nothing left. It's a large group of patients. So, that's
19 why I'm sort of getting at that.

20 Along the same lines, I would like, if you have
21 it, to see the toxicity that was observed with these
22 patients with large tumors, the stratum 3 patients.

23 DR. ELIAS: Again, as I mentioned before, we've
24 attempted to report the toxicities comprehensively across
25 the entire clinical experience. Here we do have it broken

1 out as you request, according to stratum 3 versus stratum 1
2 and 2, and stratum 1 and 2 are further subdivided into the
3 pre-amendment dosing and the post-amendment dosing.

4 This shows the most common toxicities in the
5 moderate to severe grade. And the immediate injection pain
6 is slightly less in the stratum 1 and 2 with the lower
7 dosing. The moderate to severe local pain, which is the
8 pain that can occur after the immediate injection, is also
9 slightly less as you move to the current dosing
10 indications, but it's not usually different.

11 Nausea and vomiting is slightly more severe in
12 the stratum 3 with the initial dosing, and in terms of the
13 local cytotoxic effects, the effects of local tumor
14 breakdown, they change modestly with the stratum and the
15 dosing change, particularly erosion and ulceration is a
16 little bit higher with stratum 3. Necrosis, which is
17 statistically correlated with response actually remains
18 roughly the same across these different categories. So,
19 there's a bit of a shift but not any big surprises I don't
20 think.

21 DR. LIPPMAN: Thank you for showing those data.

22 I just have two quick follow-ups to what was
23 just asked. When the issue of hospitalization versus
24 outpatient therapy was brought up, Dr. Mills said that he
25 treats all patients as an outpatient, and of course, he's

1 very experienced with this and one would expect that would
2 be the best case scenario. Of the data of the entire
3 population of patients, how many required hospitalization
4 or were hospitalized? Do you have those data?

5 DR. LEAVITT: We don't have those data because
6 most often these patients were treated in an outpatient
7 setting, but sometimes they were in hospital as a place to
8 get treatment. In Europe frequently it is easier to have
9 patients admitted to hospital rather than treat them as an
10 outpatient. There are various cultural reasons for that.
11 And even in the U.S. patients who are traveling from a
12 distance to come for therapy did get hospitalized, so that
13 we don't really have clear data that show you how
14 frequently this could have been done as an outpatient.

15 DR. LIPPMAN: I think in the briefing document
16 you indicated that they were treated as an outpatient or
17 limited hospitalization.

18 DR. LEAVITT: That's true.

19 DR. LIPPMAN: So, your answer is that most of
20 the time the hospitalization was because they were there
21 already or cultural.

22 DR. LEAVITT: That's correct. These limited
23 hospitalizations are really overnight admissions, sometimes
24 23-hour admission.

25 DR. LIPPMAN: Then one final question to follow

1 up on Dr. Przepiorka's question. I thought, when she asked
2 the question, you were going to show data on the whole
3 issue of mixed responses, not the overall. I've seen the
4 overall data that the response rate is about the same in
5 the non-most troubling tumors and the most troubling
6 tumors.

7 The question is, did you have cases, and what
8 was your data on the discordance where you had, as Dr.
9 Blayney I think brought up, a response in a non-MTT? I
10 guess more of a concern to me would be a response in the
11 MTT and a progression in the non-MTT. Do you have the data
12 presented that way? Not overall, but discordance of
13 response.

14 DR. LEAVITT: I'm sorry, I don't have those
15 summary data, but would you accept an overall view? We
16 never saw a distant progression of a treated tumor when an
17 MTT was responding. The MTT in each and every individual
18 patient was the least likely to respond of any treated
19 tumor. Now, some of that may be the nature of the tumor,
20 and some of that may simply be the treatment regimen, where
21 we asked the investigator to start and make sure that he
22 treated the MTT preferentially, so that in fact those
23 tumors may have been most thoroughly treated.

24 DR. LIPPMAN: And a related question. Was the
25 MTT always the largest tumor that the patient had?

1 DR. LEAVITT: Usually, but not always. A
2 critically placed smaller tumor, for example, near an
3 airway might have been designated as the most troublesome
4 tumor.

5 DR. NERENSTONE: Dr. Temple?

6 DR. TEMPLE: I have a few questions about what
7 the benefit that has been shown was. I guess my first one
8 is that in the middle of the study, you changed from a
9 primary endpoint of response rate, which you thought you
10 had some idea about, to a co-primary endpoint, which I
11 don't know what that means exactly, but it means you have
12 to win on it, I suppose, of clinical benefit. But you
13 didn't adjust the study size.

14 Now, it's perfectly obvious that responses are
15 going to be more obvious and show a bigger difference than
16 clinical benefit. Can you say something about why you
17 didn't change the study size?

18 DR. HOWELL: I'll ask Dr. Morgan to address
19 that.

20 DR. TEMPLE: The result of that is that no
21 single study showed any clinical benefit, and you're going
22 to ask people to look at it pooled. But why did you make
23 that necessary?

24 DR. STEWART: Well, I think you have to look at
25 the full evolution of the studies from 1994 to the

1 unblinding in the year 2000. I used the word "evolution"
2 earlier, and I think it really is the best word to use to
3 describe what happened to the study design over that period
4 of time.

5 I realize that there is some disagreement
6 that's come through in the briefing books about when
7 patient benefit became the primary endpoint, but certainly
8 our perception was, although a clinical benefit endpoint
9 was discussed, was included in the studies, and was known
10 to be very important from the time the protocols were
11 written, that it wasn't clear that this was something that
12 the agency wanted as a primary endpoint until 1997. And it
13 wasn't formally designated as "a co-primary endpoint" until
14 actually last year.

15 So, as the studies evolved, we had reached a
16 point where it would have been, I think, very awkward to
17 increase the study size. We already had some data on
18 board. We were halfway done with the studies. There's a
19 lot of statistical issues that come into play when you have
20 part of the data, even though you haven't unblinded yet,
21 and you're restating your power and recalculating the study
22 size.

23 I'd also like to point out that the issue of
24 resizing the studies, based on another or new or newly
25 recognized primary endpoint, was never an item of

1 | discussion between the agency and Matrix. It literally
2 | never came up. So, we felt there wasn't any need to do
3 | that.

4 | DR. TEMPLE: Actually adjusting sample size
5 | under those circumstances with people blind has been
6 | addressed by many statisticians, and you actually don't pay
7 | much of a price. But I understand there may have been
8 | confusion.

9 | So, let me be sure that we understand. On the
10 | patient benefit -- this is your slide 35 -- which includes
11 | both palliation and prevention, which appears to be the
12 | primary endpoint, you are not saying that either study
13 | showed a significant difference, but you do say that the
14 | combined studies showed a difference with nominal
15 | statistical significance. Is that fair?

16 | DR. HOWELL: That is correct.

17 | DR. TEMPLE: And it's not easy to tell because
18 | you don't quite do it that way, but if I look at the next
19 | slide, like slide 37, it looks as though 13 of the people
20 | who benefitted, roughly, had a palliation endpoint and most
21 | of the rest had a prevention endpoint. There seems to be
22 | some double counting and I can't quite sort it out, but is
23 | that more or less right? Because the prevention endpoints
24 | are described in figure 42, and there seem to be 26 versus
25 | 6, so that seems like a big part of the difference in the

1 overall patient benefit. Is that true?

2 DR. STEWART: Well, there was not double
3 counting in the sense that patients had a double shot.

4 DR. TEMPLE: No, I understand. But they may
5 have had both things in some cases, but only one would
6 count in your primary analysis.

7 DR. STEWART: Right. There were patients in
8 whom the primary patient endpoint was palliative, and the
9 primary physician goal, treatment goal was preventive. And
10 in the original algorithm, both the patient's primary goal
11 and the physician's primary goal were put into the
12 algorithm to contribute to patient benefit. So, if one
13 failed and the other was met, no benefit was ascribed.

14 DR. TEMPLE: But patients could never have a
15 prevention goal. That had to be generated by the
16 physician.

17 DR. STEWART: That's correct.

18 DR. TEMPLE: And to some extent that seems to
19 be driving the result. That's not a critical comment. I
20 mean, prevention is good.

21 DR. STEWART: Yes. We feel that prevention was
22 important, as has been discussed, but we also recognize the
23 agency's concern about prevention and palliation being
24 different things, and that's why we presented some of our
25 results for palliative goals only.

1 DR. TEMPLE: Okay, and then prevention is
2 presented on page 42. Not everybody had a prevention goal
3 so your numbers are down, but you're asserting a nominal
4 significance of .027 on that thing.

5 This is my last. If you then go to number 58,
6 where you talk about the FDA analysis of the palliative
7 goals, which doesn't apply to prevention goals, I'm
8 curious. I don't understand what 58 conveys to you.

9 But I first have to say, it looks as if, when
10 the endpoint was defined, nobody took into account -- and
11 we didn't suggest it to you either -- nobody considered the
12 possibility that people would get worse. So, that wasn't
13 part of the endpoint at all.

14 DR. STEWART: I think that's a fair statement,
15 except that failure of a goal negated a benefit. So, at
16 the time that the patient benefit algorithm was put
17 together in 1997, worsening was definitely considered as
18 part of the algorithm. If you had a worsening of either
19 primary goal, you couldn't be a benefitter, and that's
20 where the worsening comes in, and that is the genesis of
21 our definition of worsening as 7 or 8 days with two
22 measurements showing a worsening.

23 DR. TEMPLE: Okay, but you did on page 58 look
24 at 28-day worsening, too. You might want to look at that
25 one because at first glance, it looks very adverse, and you

1 | didn't find it so adverse and I couldn't tell why. This
2 | seems to say that in both studies about as many people got
3 | more worse on the drug as got more better on the drug. And
4 | in both cases now, they're defined with the same 28-day
5 | period of time. So, why isn't that very bad?

6 | DR. STEWART: Well, we don't think it's bad,
7 | and I'm going to ask Dr. Leavitt to address this also. Our
8 | point here was, once we leveled the playing field, by
9 | having an equivalent definition of better and worse, that
10 | the great excess of worsening which was seen in the
11 | agency's analysis essentially went away, and now we've got
12 | a balance between better and worse.

13 | I'd like to ask Dr. Leavitt to address the
14 | issue of patients of this type, when they're on treatment
15 | and what patterns of worsening and improvement are seen.

16 | DR. TEMPLE: Okay. Just to be sure we
17 | understand, this is on the same scales that palliation is
18 | looked at.

19 | DR. STEWART: Right.

20 | DR. TEMPLE: So, that means worse means they
21 | went up a point, and better means they went down a point.

22 | DR. STEWART: For the same period of time.

23 | DR. TEMPLE: And they're both for a full 28
24 | days.

25 | DR. STEWART: No. We set the goalposts at the

1 7-day rule. But now we're evaluating both better and worse
2 using the same rule.

3 DR. TEMPLE: It says first 28 days.

4 DR. STEWART: No. This is only the first 28
5 days on study. Since placebo patients tended to migrate
6 off more quickly, as has been pointed out, there are two
7 ways in which there could be an excess of worsening as done
8 in the agency's analysis. First of all, it was easier to
9 get worse than to get better because worsening only
10 required 7 days and improvement only required 28 days.

11 DR. TEMPLE: Understood.

12 DR. STEWART: And the other way that there was
13 a bias was that patients who were on CDDP/epi gel, because
14 they were responding and benefitting, tended to stay on
15 study longer, so they had a longer opportunity to have a
16 worsening of one of their goals.

17 So, by limiting the analysis to the first 28
18 days, when we had pretty equal numbers of original placebo
19 patients and original CDDP/epi gel patients on study, and
20 leveling the goalposts as to the definition of worse and
21 better, we were able to get rid of the large excess of
22 worsening, which appeared in the original table. When I
23 say get rid of it, I don't mean we waved our hands and made
24 it go away. We showed that when you do the proper
25 adjustment, that it's not there anymore.

1 DR. TEMPLE: Maybe everybody understands this,
2 and if so, Stacy, tell me to shut up. But this doesn't
3 mean someone was better for 28 days.

4 DR. STEWART: No.

5 DR. TEMPLE: That's not the better criterion
6 that you used initially. It means they were better, what?

7 DR. STEWART: To be better in this analysis,
8 you had to be better for 7 days, and to be worse you had to
9 be worse for 7 days.

10 And I'd like to point out that the reason that
11 we did this analysis was to show that there was some bias
12 in the original table, not because we're claiming that a
13 7-day benefit is clinically meaningful. We stand by our
14 claim that 28 days of improvement is what's really needed.

15 DR. TEMPLE: And you don't have people who were
16 worse for 28 days?

17 DR. STEWART: No, because typically if they got
18 worse, it meant they were progressing, and then they went
19 off study.

20 DR. HOWELL: Let me just make one last comment
21 on it. It's important to understand and be clear that when
22 you say worse, you're talking about a fraction of the
23 patients getting worse and another fraction, a different
24 fraction, getting better. This is not a within-patient
25 assessment.

1 DR. TEMPLE: No, I understand, but if it were
2 really true, which it apparently isn't, that twice as many
3 people had longstanding worsening on the drug than on
4 placebo, that wouldn't be so good. That would suggest that
5 the injections make people as much worse as they make them
6 better. But you have explained that this is a transient
7 associated with the injection, perhaps.

8 DR. HOWELL: We're just trying to get a grip on
9 the issue of, does this drug cause patients to get worse,
10 as well as some patients to get better. And the answer is,
11 no.

12 DR. TEMPLE: Well, the answer is yes, briefly.

13 DR. NERENSTONE: My question also is a little
14 bit about symptomatology. Depending on which graph you
15 look at, anywhere from 15 to 30 percent of patients had
16 nausea and vomiting, moderate to severe. Was everyone pre-
17 treated with antiemetics?

18 DR. HOWELL: No. In fact, my understanding is
19 that the vast majority did not receive any -

20 DR. NERENSTONE: But, Dr. Mills, didn't you say
21 that all of yours were?

22 DR. MILLS: The protocol did not specify the
23 investigator had to pre-med. I pre-medicated all my
24 patients, though, because like I said, platinum to me is a
25 drug you need an antiemetic for.

1 DR. NERENSTONE: Well, it's sort of an
2 important question because this drug is being touted as
3 being available for people who don't want the side effects
4 of chemotherapy. And I think certainly low-dose weekly
5 systemic platinum may have a similar episode of nausea and
6 vomiting. So, that's my question pertaining to that.

7 DR. MILLS: I don't think this is anywhere near
8 that. Even in this trial, if you looked at severe nausea
9 and vomiting, I think it was only 3 to 4 percent. That was
10 all grades of nausea and vomiting as an AE, which is not
11 the same as the platinum nausea and vomiting that we deal
12 with.

13 DR. NERENSTONE: Do you have any data about the
14 duration of the nausea and vomiting? I believe that you
15 described it as moderate to severe.

16 DR. MILLS: I'd have to ask the company for
17 that data.

18 Dr. Wenig, I think, could comment on his
19 patients that he treated.

20 DR. WENIG: I can tell you that the patients
21 that I treated and the other patients treated by the
22 population of treating physicians who come from a surgical
23 background did not pre-medicate their patients at all. I
24 certainly didn't see anywhere near any levels of nausea and
25 vomiting in any of the patients that are described.

1 DR. NERENSTONE: Another question I have about
2 toxicity, and I understand that there are low levels, but
3 there are some levels of platinum. Did anyone look at pre-
4 treatment creatinines, or creatinine clearances as a
5 preliminary for allowing patients on trial? And do you
6 have any data in people who you would assume would have
7 very limited creatinine clearances in terms of toxicity?

8 DR. HOWELL: Yes. Let me let Dr. Leavitt
9 address the issue of whether that was prospectively called
10 out in the protocol. But let me also comment that the area
11 under the curve for exposure for the systemic circulation
12 is in the range of 4 percent of what you get when you give
13 a standard dose intravenously. So, issues of renal
14 function really become pretty minor unless the renal
15 function is severely impaired. You're just not getting
16 that much systemic exposure.

17 Now, it doesn't take a whole lot of platinum in
18 your systemic circulation to give you some nausea and
19 vomiting, but when you look at the area under the
20 concentration times time curve, the overall exposure is way
21 below what you would expect to threaten the kidney in any
22 way.

23 DR. NERENSTONE: Right. I'm just worried about
24 what Dr. Lippman pointed out, which is that at the higher
25 level of doses, with the bigger tumors, when you open this

1 up to the general population, those patients perhaps, not
2 at your recommendation, but may in fact go on trial. They
3 really are going to see higher doses than perhaps the
4 optimal patient would receive. And the people who are
5 going to be put on these trials are going to be the elderly
6 debilitated patients who have very limited creatinine
7 clearances. I'm just wondering if you had a level of
8 creatinine clearance that you would not want to see
9 patients on trial, and whether any data has been generated
10 about the toxicity.

11 DR. ELIAS: Yes. The protocol eligibility
12 criteria excluded patients with serum creatinines or
13 creatinine clearances more than 1.5 above the upper limits
14 of normal, and we would adhere to those recommendations in
15 the future.

16 With respect to changes in creatinine on
17 protocol, these were tracked, and actually numerically
18 there were more patients whose creatinines got better after
19 treatment than got worse.

20 With respect to antiemetic medications, a
21 subpopulation of patients at some point during the study
22 did get antiemetics. It's not possible to discern a
23 pattern with respect to the AEs that were reported. In
24 other words, in patients who received antiemetics, some of
25 them didn't have nausea and vomiting reported, some of them

1 | did. It's hard to ferret out because some of the patients
2 | were previously exposed to chemotherapy, and in some
3 | instances it was the physician's routine to give
4 | antiemetics, and in some instances antiemetics were given
5 | in response to an episode. So, it's hard to exactly ferret
6 | out a sequence across the whole study, but only a
7 | subpopulation of the patients actually received antiemetics
8 | while on treatment.

9 | DR. NERENSTONE: And one last question, which
10 | is, for patients who required chemotherapy for non-
11 | indicator lesions, how was the duration of response
12 | determined for the lesions that were injected? In other
13 | words, at what point are they considered no longer to be
14 | responding to the intralesional treatment?

15 | DR. LEAVITT: I'll give you a quick answer to
16 | that. We censored the duration of all responses when there
17 | was any confounding therapy, such as an exposure to
18 | systemic chemotherapy or any other kind of therapy that
19 | might have confounded the duration of response. That's
20 | when we cut it.

21 | DR. NERENSTONE: I think what we'd like to do
22 | now is take a very brief 5-minute break. I'd like
23 | everybody back at 4:40.

24 | (Recess.)

25 | DR. WILLIAMS: Madam Chairman, members of the

1 | committee, ladies and gentlemen.

2 | This slide presents the outline of the FDA
3 | presentation. I will start off the presentation with the
4 | regulatory background. Then Dr. Frykman will present the
5 | medical officer findings, followed by Dr. Sridhara's
6 | statistical comments. Finally, I will summarize the FDA
7 | findings and introduce the questions to the committee.

8 | First, I'd like to commend Matrix for
9 | undertaking these studies -- randomized placebo-controlled
10 | trials in head and neck cancer is certainly an unusual
11 | phenomenon -- and also for having the courage to try to
12 | explore new endpoints to define clinical benefit in head
13 | and neck cancer. We've had a very good working
14 | relationship, I think, both through the years and also
15 | throughout this NDA review.

16 | This slide recognizes the FDA review team.
17 | This includes reviewers from a number of disciplines, and
18 | is led by project manager Dianne Spillman.

19 | Drug approval usually requires two adequate and
20 | well-controlled studies demonstrating the drug is effective
21 | and also safe for its intended use. The efficacy
22 | requirement is from a 1962 law that required substantial
23 | evidence of efficacy and stated that this evidence must
24 | come from adequate and well-controlled investigations.

25 | FDA subsequently interpreted the 1962 amendment

1 to mean that changes defined as efficacy must have clinical
2 meaning. That is, they must represent clinical benefit.
3 The laws and regulations give no firm definition of
4 efficacy or clinical benefit. This judgment is left to the
5 FDA.

6 As the ODAC is faced with giving FDA advice
7 today on the meaning of clinical benefit in head and neck
8 cancer, it seems appropriate for us to review the FDA's
9 approach to clinical benefit and evaluation of oncology
10 drugs in recent years.

11 In the early 1980s, FDA approved cancer drugs
12 based on response rate. In the mid-1980s, upon the advice
13 of ODAC, the FDA determined that response rates should not
14 generally be the sole basis for approval. The possible
15 benefit associated with partial response did not
16 necessarily outweigh the substantial toxicity of cancer
17 drugs. And correlation between tumor response and survival
18 was not well established. The new FDA position required an
19 improvement in survival, or in patient symptoms for
20 approval.

21 Subsequently, however, the FDA did on some
22 occasions base approval on other endpoints. Their
23 acceptability was determined on a case-by-case basis, by
24 FDA oncologists, with advice from ODAC.

25 The FDA stated that under selected

1 | circumstances impressive tumor-related outcomes could be
2 | considered clinical benefit. For instance, an improvement
3 | in disease-free survival can be a valid endpoint for an
4 | adjuvant setting if a large fraction of recurrences are
5 | symptomatic. Complete responses of reasonable duration may
6 | represent effectiveness in some diseases such as leukemia.
7 | The appropriateness of reliance on response rate should
8 | take into consideration the duration of response and the
9 | toxicity of treatment. Finally, the legitimacy of response
10 | rate as an endpoint is enhanced by correlation with
11 | improvement in tumor-related symptoms.

12 | Drug approvals for some indications are of
13 | particular interest. For instance, cutaneous responses
14 | were the basis of approval for drugs for Kaposi's sarcoma,
15 | and cutaneous T-cell lymphoma and were considered clinical
16 | benefit because the lesions are visible to patients and
17 | responses were thought to be of palliative benefit, at
18 | least partially based on cosmesis.

19 | Over the past 15 years, FDA has encouraged
20 | development of primary and secondary endpoints to evaluate
21 | patient symptoms, and several cancer drugs have been
22 | approved based on pain and morbidity endpoints. In 1995
23 | Photofrin was approved for photodynamic therapy in
24 | completely esophageal cancer. In 1998 approval was
25 | extended to completely or partially obstructing

1 endobronchial non-small cell lung cancer. FDA reviewers
2 relied on patient-reported improvements in symptoms of
3 obstruction to determine that luminal responses were
4 clinically meaningful. In 1996 mitoxantrone was approved
5 for treatment of advanced prostate cancer, based primarily
6 on improvement in pain demonstrated in randomized
7 controlled trials.

8 So, when FDA met with the applicant in 1994 and
9 1995, the FDA position was that shrinkage of tumor from
10 local injection of drug into a head and neck cancer did not
11 necessarily represent clinical benefit. Randomized
12 controlled trials were recommended to demonstrate the
13 responses were associated with patient benefit.

14 Because patients with head and neck cancer have
15 such a variety of problems, FDA suggested identifying the
16 one primary problem in each patient and documenting whether
17 it got better. This would address a couple of problems in
18 most quality of life analyses. First, because only one
19 main problem is specified, one need not worry about the
20 problem of multiple endpoints. Second, this design
21 requires that all patients entered into the study actually
22 have the problem that is being assessed.

23 FDA also suggested that objective tumor
24 responses should correlate strongly with measures of
25 clinical benefit. This correlation would help support the

1 | legitimacy of a clinical benefit endpoint and would support
2 | the clinical relevance of tumor responses.

3 | As the sponsor finalized the protocol, FDA
4 | reviewers communicated a couple of points that are
5 | important for us to consider today. First, FDA was
6 | skeptical about the preventive goals. The reviewer stated
7 | the sponsor would have to provide convincing evidence that
8 | without treatment these events would indeed have happened
9 | within 28 days. FDA reviewers have not received such
10 | assurance, and furthermore, as you will hear during the
11 | FDA's statistical presentation, the NDA data show that
12 | differences between the study arms, the preventive goals
13 | are entirely due to differences in dropout patterns between
14 | the study arms; that is, due to patients dropping out more
15 | often on the placebo arm before data 28 than on cis gel.
16 | If you look at the events that were to be prevented, there
17 | were actually more events documented in the cisplatin gel
18 | arm. For this reason, we have not accepted preventive
19 | goals in our analysis. Our analysis is limited to
20 | palliative goals.

21 | FDA reviewers also communicated to the sponsor
22 | their uncertainty whether a 1-point change on the proposed
23 | palliative scale represented a clinically significant
24 | change. The sponsor has provided information purporting to
25 | support the claim, and we seek ODAC's opinion on whether a

1 1-point change on the palliative scale is clinically
2 significant. In our analyses, we present clinical benefit
3 data, including the 1-point change, pending ODAC's advice
4 on this point.

5 That concludes my introductory comments. Dr.
6 Frykman will now present the FDA clinical review, and Dr.
7 Sridhara will provide the FDA clinical analysis. Then,
8 finally, I will return to summarize and to introduce the
9 questions.

10 DR. FRYKMAN: There were two key objectives
11 around which both studies, 414 and 514, were designed.
12 One, to compare the objective response rate, active versus
13 placebo drug, and two, to assess the achievement of a
14 primary treatment goal.

15 The key features of the design included
16 stratification based on the most troublesome tumor size,
17 block randomization, double-blinding, and placebo-
18 controlled. The sample size was based on an appropriately
19 powered design to detect a difference in objective response
20 rate between the active and placebo gel.

21 Patients were enrolled, as you previously
22 heard, on three strata, and I think I won't continue on
23 with that.

24 This slide lists six studies that were
25 submitted in support of IntraDose for head and neck cancer.

1 I will review briefly the first two, with a few comments
2 about the pharmacokinetic findings at the end.

3 Dr. Williams previously referred to
4 correspondence with the company in 1994 when the initial
5 discussion of clinical benefit first arose. Partway during
6 enrollment into studies 414 and 514, the applicant and the
7 division met to clarify the division's views on the
8 endpoints for both studies. Symptomatic response was
9 strongly recommended as a primary efficacy endpoint.
10 Despite the studies being designed to detect a difference
11 in objective response rate, the applicant and the division
12 reached agreement that the primary efficacy analysis would
13 be symptom improvement. Tumor responses would play a
14 supportive role.

15 As the studies closed, additional clarification
16 was made at the request of the applicant. The FDA
17 clarified that a strong correlation would be required
18 between a patient's tumor objective response and any
19 palliative benefit claimed.

20 Finally, a 1-point improvement in palliative
21 benefit, as measured by the treatment goal questionnaire,
22 would not necessarily provide sufficient clinical evidence
23 for clinical benefit.

24 During the initial accrual to both studies, an
25 appreciation for the difficulty of administering a fixed

1 dose of gel into certain tumors arose. The problem that
2 was noted was the inability of some tumors to accommodate
3 to protocol-specified volume. At times the correct volume
4 could not be injected, and when it was completely instilled
5 inside the tumor nodule, a fraction would leak out or
6 reflux back out of the needle track.

7 The applicant, therefore, amended the dosing
8 regimen and technique. Prior to amendment 5, as you've
9 heard, the protocol-specified dose was .5 ml of gel per cc
10 of tumor volume. This dose was based on the volume of the
11 tumor at the first visit. The dose was administered by a
12 single injection and bolus administration into the tumor.
13 A total of 62 patients were enrolled at the time of the
14 study amendment.

15 Following amendment 5, however, the dose was
16 reduced by 50 percent to .25 ml of gel per cc of tumor
17 volume. This time, however, the volume was recalculated at
18 each visit just prior to injection. In addition, the
19 injection technique was changed from a single injection to
20 a fanning or a grid technique utilizing multiple needle
21 tracks. 163 patients were enrolled following this
22 amendment.

23 The eligibility criteria have been previously
24 discussed, and I will go over just a few of the more
25 important ones. The patient population included by

1 refractory and recurrent squamous cell carcinoma of the
2 head and neck, which had been treated by as few as one of
3 the following modalities: surgery, chemotherapy,
4 radiotherapy, or alpha interferon. Either primary or
5 metastatic lesions were allowed, although systemic disease
6 was excluded. Patients with a known history of cardiac
7 arrhythmias were also excluded owing to the epinephrine
8 component of the gel.

9 Each study was identical in design and was
10 comprised of three phases: a treatment phase lasting 10 to
11 12 weeks, a follow-up phase that lasted 5 months, and an
12 extended follow-up phase for an unspecified duration.

13 The treatment phase was comprised of two
14 periods: a treatment period and an evaluation period. The
15 treatment period lasted 6 to 8 weeks, and it was during
16 this time that the patients received six injections of
17 blinded drug. The evaluation period was for assessment
18 only, and although patients were seen weekly, no study drug
19 was administered.

20 Following the treatment phase, patients entered
21 into a follow-up phase in which they were seen monthly
22 without injections. If local progression occurred,
23 patients would become eligible for entering into extended
24 follow-up, in which a higher dose of the open-label drug
25 could be administered or concomitant therapy as well. The

1 FDA based no efficacy considerations on any responses or
2 clinical benefit that occurred during this phase.

3 As you previously heard, study 414 was a North
4 American study, which was conducted in 44 centers in the
5 U.S. and Canada over an approximately 5-year period. Study
6 514 was a predominantly European study in 28 centers over
7 approximately the same 5-year time period.

8 With regard to baseline demographics of the
9 enrolled population, the arms of each individual study were
10 reasonably well balanced in terms of age, Karnofsky
11 performance status, histological grade, prior therapy and
12 ethnicity. This table and the following one reveal the
13 degree to which patients remained in the treatment period
14 of the blinded phase. A differential dropout is noted at
15 treatments four, five, and six, with no patients remaining
16 on the placebo arm at the end of six injections, versus 16
17 percent on the active arm. This finding has implications
18 regarding blinding and forms some of the basis upon which
19 the division discounted the preventive goal as suggesting a
20 clinical benefit. Dr. Sridhara will address this issue in
21 her remarks.

22 Similar results are seen in study 514 where the
23 treatment conformity decreases to 42 percent in the active
24 arm and 17 percent in the placebo arm at the end of six
25 injections.

1 This table and the next table present the
2 reasons why patients terminated enrollment in the study.
3 Approximately one-quarter of the patients did so for
4 systemic progression of their disease. This is an
5 important number to keep in mind, as Dr. Sridhara will
6 briefly mention the median survival of this patient
7 population.

8 Another 20 percent terminated their enrollment
9 due to progressive disease of the target tumor. What is
10 not included in this table is the number of patients who
11 progressed locally, not systemically, in the form of
12 worsening, co-existing lesions, or by the appearance of new
13 lesions not present at the initial visit.

14 In study 514, more than half of the patients,
15 the top two, were terminated from the study for progression
16 either systemically or locally, again raising the same
17 issue of local regional progression in the presence of a
18 remitting lesion that has received serial injections.

19 The key efficacy results are shown here and
20 include objective response only, clinical benefit, and
21 clinical benefit in the presence of an objective response.
22 Of the 62 patients randomized to the active arm in study
23 414 in strata 1 and 2, there were 20 who achieved an
24 objective response which was required to be maintained for
25 28 days with at least a 50 percent volume decrease.

1 This finding must be viewed in the context of
2 four important factors. The first one is frequent dosing
3 errors that were noted by the agency in its review. The
4 second is that this response rate is a local response rate
5 and may not be analogous to what we're used to with
6 systemic objective response rates. Thirdly, in some cases
7 a tumor response was noted in a field of newly appearing
8 lesions. And fourth, responding lesions tended to be on
9 the small side.

10 The dosing errors which arose from several
11 sources were so numerous that only 3 of the 20 patients who
12 responded actually received IntraDose at the protocol-
13 specified dose and manner. A description of these errors
14 will follow two slides after the same display for study
15 514.

16 Caution must also be exercised in interpreting
17 this rate of objective response. Again, this is a local
18 response and may not follow analogously to systemic
19 response to the same degree. Of the 20 responding lesions,
20 12 were in stratum 1, with a median baseline tumor volume
21 of 1.6 cc's.

22 Total clinical benefit was noted in 3 of the 51
23 patients for yielding a rate of 5.9 percent. The number of
24 patients receiving clinical benefit in the presence of
25 objective response was 2 out of the population of 51 who

1 | had chosen a palliative benefit treatment goal for a
2 | clinical benefit and objective response. The rate of this
3 | is 4 percent, and this represents the primary efficacy
4 | endpoint of this study.

5 | The efficacy results from the European study
6 | showed objective responses in 13 of the 57 patients, for a
7 | response rate of approximately 23 percent. Only 6 followed
8 | the protocol-specified dose and schedule. Again, this
9 | represents a local tumor objective response rate in only
10 | the tumor that was injected. Of the 13 responders, 9 came
11 | from stratum 1, with a median baseline tumor volume of 2
12 | cc's.

13 | A total clinical benefit rate of 10 of 54, or
14 | 19 percent, was noted in this study. There were 5 patients
15 | in this population of 54 whom the division confirmed as
16 | having achieved both an objective response and palliative
17 | clinical benefit.

18 | The applicant and the division, as early as
19 | 1994, wrestled with the differences and the color between
20 | the clear placebo gel and the yellow-colored active gel.
21 | Dr. Leavitt has referred to the efforts that the applicant
22 | undertook to maintain the blinding. Agreement with the
23 | division was reached that a yellow colored film or sleeve
24 | would be wrapped around the barrel of the administration
25 | syringe by the investigational pharmacy to maintain the

1 | blind of the injecting physician.

2 | During the review of the study, there were
3 | several findings that independently led to question about
4 | the adequacy of this blind. Each of the findings alone
5 | does not necessarily raise concerns, but taken as a whole
6 | suggests that there is a potential for the study to have
7 | not maintained its double-blind feature. Concerns we noted
8 | during the review include differential local toxicity,
9 | differential dropout, local hair loss, and a yellow
10 | discolored eschar.

11 | There were also a number of concerns that arose
12 | with the method of blinding. Could the yellow color be
13 | detected as the gel is injected through the tip of the
14 | syringe? Could the yellow color of the gel be detected
15 | upon refluxing back out of the tumor and then wiping it
16 | with a clean, sterile white gauze? Could the investigator
17 | readily observe a yellow color if a small amount of the
18 | material was expressed into the gauze prior to injecting?
19 | And how tightly was the yellow plastic sleeve wrapped
20 | around the syringe? Might it be removed by the
21 | investigator to improve tactile sense and dexterity
22 | immediately prior to the injection, and thereby unblind the
23 | investigator? In each of these scenarios we do not know
24 | how often, if ever, they occurred.

25 | As mentioned a few moments ago, there are a

1 | number of sources of dosing error that were noted in the
2 | study arising from errors in measurement, errors in
3 | calculation, and errors in administration. The errors in
4 | measurement are similar to those that we confront when
5 | trying to determine if a lesion on CT has regressed to the
6 | requisite amount to be declared a partial response. This
7 | uncertainty increases with small lesions and is confounded
8 | by local tissue disruption, such as seen in this study, by
9 | the gel, either placebo or active gel, in terms of local in
10 | duration, necrosis, erosion, and so forth.

11 | Calculation errors arose from using the
12 | incorrect gel-tumor ratio, missing tumor dimensions, and
13 | even injections in the absence of any tumor measurements.

14 | Finally, administration errors resulting from
15 | the reflux of the gel out of the tumor, and/or the PI's
16 | discretion to use other than the protocol-specified dose,
17 | further confounded attempts to administer the required
18 | doses correctly.

19 | This histogram represents the relative
20 | frequency that dosing errors occurred, and the magnitude of
21 | these errors. On the y axis is the number of doses. The x
22 | axis shows varying ranges of dosing errors in the percent
23 | of the planned dose. Doses smaller than the protocol-
24 | specified dose are on the left. The central four bars
25 | represent the number of doses that were within 25 percent

1 of the expected dose, based on the available tumor
2 dimension. This slide represents all doses in study 414.
3 The large bar on the left represents patients who should
4 have received an injection, but did not because of
5 investigator discretion, missed appointments, or
6 unacceptable local toxicity.

7 The bar on the far right represents the
8 injections in which the dose was calculated incorrectly
9 from either a mathematical error or the use of an incorrect
10 gel-tumor ratio, which was changed with amendment five.
11 Note that there is substantially more underdosing than
12 overdosing, and this is mostly the result of reflux, the
13 tumor being unable to accommodate the specified volume, and
14 the investigator's discretion in using a smaller dose than
15 planned.

16 This histogram for study 514 similarly shows
17 the deviations from the protocol-specified or planned dose
18 in the same manner as displayed in the previous slide for
19 study 414. There was one notable difference from the
20 previous histogram. A larger portion of patients in the
21 central four bars appear to have received close to or
22 exactly the correct dose. There remained, however, a still
23 sizeable fraction of administrations that were incorrect or
24 did not occur at all. As noted in study 414, more patients
25 were underdosed than overdosed.

1 Within these studies the reviewers noted a
2 herculean effort by the applicant and the investigators to
3 collect serial local toxicity and palliative benefit data
4 at each visit. We have, therefore, a detailed record over
5 time of each responding or benefitting patient with regard
6 to their unique palliative benefit, tumor size, and local
7 toxicity assessments. Because of these extensive data
8 about the local tumor, we could retrospectively evaluate
9 the totality of each patient's data for integrity and
10 internal consistency.

11 Examples of the inconsistencies shown on this
12 slide were noted and speak to the questionable integrity of
13 some of the clinical data in several claimed cases of
14 clinical benefit. These data will not be shown at this
15 time. They are available if needed.

16 The findings limit our confidence that, number
17 one, a 1-point change in the specified treatment goal was
18 reliably detected in these studies, and number two, that a
19 1-point change on the clinical benefit scale actually
20 represents meaningful palliative benefit.

21 The applicant collected data as requested by
22 the division on the nature, severity and duration of the
23 local toxicity. You all have seen this data presented
24 previously and I will skip the rest of this slide.

25 The final aspect of the safety portion of this

1 presentation is a brief review of the systemic adverse
2 events. The applicant has presented information in the
3 briefing document about the six cases of cerebrovascular
4 accidents that occurred in study 414. Additionally, one
5 incident of complete blindness occurred in study 514. The
6 investigators' attribution in this case was that it was
7 directly related to IntraDose administration. We conclude
8 that inadvertent direct injection into vital organs such as
9 the carotid artery, the eye, or the optic nerve cannot be
10 excluded.

11 The final issue that I would like to briefly
12 address is the degree that the cisplatinum remained in the
13 local tumor following injection. No specific assays of
14 intratumoral cisplatinum levels were performed. However,
15 we can glean a sense of how localized the cisplatinum
16 remained by assaying for systemic exposure, and this was
17 the point of study of the pharmacokinetic study.

18 Our clinical pharmacology colleagues made two
19 important observations and drew one important conclusion
20 from this study. The important observation is that the
21 pharmacokinetics of the cisplatinum is highly variable, up
22 to 100 percent coefficient of variation for the AUCs after
23 intratumoral administration.

24 Secondly, the time to peak plasma
25 concentration, or the Tmax, in the 16 patients range from 5

1 | minutes to 24 hours, with a median of 1.5 hours. Their
2 | conclusion was that dose normalized exposure to cisplatin
3 | after intratumoral administration was similar to
4 | intravenous exposure.

5 | In summary, I would like to highlight some of
6 | the key issues that arose from a review of the clinical
7 | data derived from studies 414 and 514. There were numerous
8 | errors and deviations from the protocol-specified dose and
9 | schedule that raise questions about the adequacy of the
10 | conduct of both studies, especially in study 414.

11 | Differential toxicity and dropout and other
12 | incidental findings in the presence of two medications with
13 | known color differences raise questions about how tightly
14 | the blind was maintained.

15 | Additional inconsistencies were noted and
16 | raised questions about the integrity of the clinical data.

17 | The response rates were modest, in the 20 to 30
18 | percent range, and objective responses, tightly correlated
19 | with palliative benefit, was seen in 9 percent in the
20 | European study and a rate of 4 percent in the U.S. study.
21 | Keep in mind that these were local, not systemic responses
22 | from a locally injected cytotoxic drug and that smaller
23 | lesions appeared to respond better.

24 | Local toxicity, as expected, was generally mild
25 | and moderate, but occasionally severe and increased in

1 | severity and frequency with additional treatments compared
2 | to placebo gel. Seven devastating adverse events were
3 | noted in the safety database limited to these two studies.
4 | Direct injection into vital structures cannot be excluded
5 | and may represent a substantial safety risk.

6 | Finally, we ask the committee during their
7 | deliberations to consider the overall value of IntraDose
8 | for shrinking a target tumor in a field of newly appearing
9 | and/or progressing lesions in the local and/or regional
10 | area.

11 | I would like to thank you for your attention
12 | and will turn the podium over to Dr. Sridhara, who will
13 | cover the FDA's statistical findings.

14 | DR. SRIDHARA: Thank you, Dr. Williams and Dr.
15 | Frykman.

16 | This is a joint statistical review by Ms. Choi
17 | and myself.

18 | There are two major areas of concern.

19 | The two double-blinded, randomized studies were
20 | required to demonstrate efficacy with respect to two co-
21 | primary endpoints, namely objective tumor response and
22 | clinical patient benefit. The understanding was that both
23 | endpoints should demonstrate efficacy and thus not require
24 | adjustment of type 1 error for multiple endpoints. Both
25 | the studies failed to demonstrate clinical patient benefit.

1 The second concern is regarding the association
2 between objective tumor response and patient benefit in
3 terms of prediction of benefit from response and validating
4 benefit measure. The association between tumor response
5 and patient benefit is weak.

6 In the next couple of slides, I will focus on
7 the primary endpoint of objective most troublesome tumor,
8 or MTT, response. It is to be noted that both studies were
9 sized based on MTT response as the endpoint. However, we
10 never expect any substantial tumor response with placebo
11 and, therefore, we are most likely to find significant
12 tumor response with any active cytotoxic drug when compared
13 to placebo.

14 This slide shows the sponsor and FDA analysis
15 of tumor response in the U.S. study 414. Per FDA analysis,
16 the tumor response in the IntraDose arm was 32 percent.
17 Furthermore, 12 of the 20 objective responses in the
18 IntraDose arm were in stratum 1, or in patients with
19 smaller lesions.

20 This slide describes the sponsor and FDA
21 analysis of study 514. Per FDA analysis, the response rate
22 was 23 percent in the IntraDose treatment arm. 9 of the 13
23 objective responses in the IntraDose arm were in stratum 1
24 and in patients with less than or equal 5 cubic centimeter
25 lesions.

1 This is the survival graph of the IntraDose
2 versus placebo with the combined data of both the studies.
3 There is no difference between the two arms and the
4 estimate of median survival was about 3 months in both the
5 arms. As expected, the local treatment response does not
6 seem to translate to survival benefit.

7 I will now present analysis of the primary
8 endpoint of clinical patient benefit.

9 The patient benefit was measured on a
10 preselected treatment goal using the questionnaire designed
11 by the sponsor. This questionnaire has only been used in
12 the two studies under consideration here. The validation
13 of this instrument was conducted by the sponsor with only
14 15 patients and cannot be considered as adequate.

15 The treatment goal, a palliative goal or
16 preventive goal, was selected by the investigator prior to
17 the randomization for each patient. The patients were also
18 encouraged but not required to select a goal.

19 Furthermore, per protocol and sponsor analysis,
20 the patient benefit is based on the investigator selected
21 treatment goals, palliative or preventive. The palliative
22 goals were wound care, pain control, abilities to see, hear
23 or smell, physical appearance, obstructive symptom, and
24 mobility. The preventive goals were prevention of invasion
25 of vital structure or blood vessels, prevention of

1 | obstruction, or prevention of tumor breaking through the
2 | skin.

3 | A post hoc patient benefit algorithm has been
4 | used by the sponsor to include patient assessment.
5 | However, it should be noted that in the case of the
6 | preventive goal, the patient could not contribute to the
7 | assessment of this benefit.

8 | Furthermore, the two treatment goals,
9 | palliative and preventive goals, were measured on different
10 | scales: palliative goal on a 4-point scale, whereas
11 | preventive goal, on a 2-point scale. Combining these two
12 | scales implies that a change of score from 4 to 3 or 2 to 1
13 | on the palliative scale is the same as met in the
14 | preventive scale. This combining of two different scales,
15 | one measuring symptom improvement and the other measuring
16 | progression, is questionable.

17 | The sponsor has also defined a 1-point decrease
18 | for a duration of 4 weeks to be a benefit for the patient,
19 | and as mentioned earlier by Dr. Williams, this is an issue
20 | that needs to be discussed.

21 | Lastly, there was no common treatment goal
22 | among the patients.

23 | This is the algorithm the sponsor has used to
24 | combine the investigator and patient assessments. If both
25 | the patient and the investigator recorded a benefit, or if

1 either of them recorded a benefit and the other recorded a
2 no change, then the patient was counted as a benefitter.
3 Note that particularly in the case of preventive goals, in
4 most cases the patient's assessment was missing. Thus, it
5 was essentially the investigator's call on the preventive
6 goal assessment.

7 These are the results of the sponsor analysis,
8 which includes palliative and preventive goals in assessing
9 patient benefit. Clearly both studies individually did not
10 demonstrate significant benefit over the placebo. In the
11 pooled analysis of both studies, there is borderline
12 significance.

13 However, pooled analysis is not acceptable when
14 both studies have failed to demonstrate clinical benefit.

15 Pooling also inflates type 1 error.

16 Furthermore, even though in both the studies
17 the plan was to accrue patients in a 2 to 1 ratio of
18 IntraDose to placebo, in fact in the U.S. study, the ratio
19 was 2.6 to 1 and in the Europe study, it was 1.5 to 1.
20 Therefore, pooling these two studies will cause imbalance
21 in randomization.

22 There is evidence that the patient populations
23 were not the same in the two studies, for example, in terms
24 of prior therapy, age, and performance status.

25 The selection pattern of treatment goals by the

1 | investigators varies between the two studies with more
2 | preventive goal as the primary selected goal in the U.S.
3 | study compared to the Europe study.

4 | Pooled analysis can only be used as supportive
5 | evidence and not as primary evidence. At best, this can
6 | only be considered as one body of evidence.

7 | This chart describes the number of treatments
8 | received in both treatment arms in study 414. The blue
9 | bars represent the IntraDose arm and the red bars represent
10 | the placebo arm. Clearly the dropout pattern in the two
11 | arms are different with no patients receiving six
12 | treatments in the placebo arm.

13 | This chart describes the number of treatments
14 | received in both the treatment arms in the Europe study
15 | 514. As in the U.S. study, the dropout pattern in the two
16 | arms are different with only 17 percent of the patients
17 | receiving all six treatments in the placebo arm versus 42
18 | percent of patients receiving all six treatments in the
19 | IntraDose arm.

20 | In the U.S. study, the investigators selected
21 | in 50 percent of the patients preventive goal as the
22 | primary treatment goal, that is, in 31 of the 62 patients.
23 | Here not met is the occurrence of an event, that is, the
24 | event where the patient's tumor has invaded a vital
25 | structure of a blood vessel or the tumor is obstructing a

1 structure or the tumor has broken through the skin. In the
2 U.S. study, per investigator assessment, in 13 percent of
3 patients, there as an event or failure, whereas there were
4 none in the placebo arm.

5 Furthermore, the category "same" is when
6 patients could not be assessed as either met or not met
7 probably because of dropout. In other words, almost 50
8 percent of the patients in both the studies in the placebo
9 arm could not be assessed for the achievement of preventive
10 goal because of dropouts.

11 Thus, the preventive benefit assessment was
12 discredited by the reviewers, as mentioned earlier by Dr.
13 Williams, because of the differential pattern of dropout
14 between the two treatment arms which could potentially bias
15 investigator assessment. This could also potentially cause
16 unblinding, which was addressed earlier by Dr. Frykman.
17 Essentially these preventive scores are not interpretable.
18 In fact, 13 percent of the patients in the IntraDose
19 treated arm in the U.S. study had an event versus none in
20 the placebo arm.

21 Also, we do not have a baseline estimate of the
22 incidence of these events in an 8- to 12-week time period
23 in this patient population to compare it to a baseline
24 incidence rate.

25 As seen above, in the U.S. study in 50 percent

1 of the patients, the investigator selected preventive goal
2 as the primary goal.

3 Further discussions will, therefore, focus only
4 on palliative goal assessment. In study 414, the
5 investigator selected in 31 of the 62 IntraDose-treated
6 patients palliative goal as the primary treatment goal. A
7 negative score here indicates improvement or benefit in
8 symptom, and a positive score indicates worsening of the
9 symptom.

10 In this study only 1 patient, or 3 percent, had
11 a benefit, if a change in score by 1 point is considered as
12 a benefit, versus 6 patients, or 19 percent, who got worse
13 on the very endpoint of interest. However, most of the
14 patients, or 74 percent of the patients, did not have any
15 change in their symptoms in both the arms.

16 In study 514, the investigator selected in 46
17 of the 57 IntraDose-treated patients palliative goal as the
18 primary treatment goal. In this study 7 patients, or 15
19 percent, in the IntraDose-treated arm appear to have
20 benefit versus 8 patients, or 17 percent, who got worse on
21 the very endpoint of interest. Again, the majority of the
22 patients, or 67 percent of the patients, did not have any
23 change in their symptoms in both the arms.

24 The sponsor did talk about the worsening, that
25 it was only a 7-day period versus an improvement for 28

1 | days. However, it should be kept in mind that these were
2 | two consecutive measurements that were made for the
3 | worsening, and it's understandable that if somebody is
4 | worsening, that you cannot keep them for 28 days in the
5 | worsening score itself.

6 | This is the FDA analysis of palliative benefit.
7 | Since we have discredited the preventive goal assessment,
8 | we analyzed the palliative goal benefit using both the
9 | patient or investigator assessments. A decrease in
10 | palliative goal score per patient or investigator
11 | assessment was scored as a decrease in score leading to a
12 | least conservative analysis of palliative goal assessment.

13 | In this table, the first set of analyses is
14 | assuming that a change in score by a scale by 1 point or
15 | more to be clinically meaningful. Even in this least
16 | conservative analysis, it is of concern that in the U.S.
17 | study patients got worse four times more than those who
18 | felt better in the IntraDose-treated arm. In contrast, in
19 | the placebo arm, patients got worse two times more than
20 | those who felt better. Most of the patients by this
21 | analysis also did not have any change in symptom score.

22 | The appropriate tests, Wilcoxon rank sum test
23 | or JT test, were conducted to test the difference between
24 | the two treatment arms which accounted for the categorical
25 | classification of patients into three categories: better,

1 | worse, and no change. There was no significant difference
2 | between IntraDose and placebo with respect to patient
3 | palliative benefit in this U.S. study by both of these
4 | tests.

5 | In the sponsor's analysis, benefit is treated
6 | as a binary outcome not accounting for patients with
7 | worsening of symptoms and used Fisher's exact test to test
8 | the difference between the two arms. This is not an
9 | appropriate analysis. For purposes of illustration only,
10 | the p value using this method is also presented in this
11 | table.

12 | Furthermore, the second set of results
13 | presented here is assuming that a change in score by a
14 | scale of 2 points or more to be clinically meaningful. In
15 | this case there were only 4 percent who felt better in the
16 | IntraDose, and no patients had benefit in the placebo arm.

17 | As in the previous slide, in this table the
18 | first set of analyses is assuming that a change in score by
19 | a scale of 1 point or more to be clinically meaningful. In
20 | this least conservative analysis, as observed in the U.S.
21 | study, in this Europe also 22 percent got worse compared to
22 | 19 percent who felt better in the IntraDose-treated arm.
23 | Again, the majority of the patients did not have any change
24 | in symptom score.

25 | There was no significant difference between

1 IntraDose and placebo with respect to patient palliative
2 benefit in the Europe study using the appropriate tests,
3 Wilcoxon rank sum test or the JT test. For purposes of
4 illustration only, the p value using the Fisher's exact
5 test and treating benefit as a binary outcome is presented
6 in this table. This is not an appropriate test as it does
7 not take into account a third category of worsening of
8 symptoms.

9 Furthermore, when the two studies were pooled
10 and data analyzed using the Wilcoxon rank sum test or the
11 JT test, there was no significant difference between the
12 IntraDose and placebo arms.

13 The second set of results presented in this
14 table is assuming that a change in score by a scale of 2
15 points or more to be clinically meaningful. In this case
16 there were only 4 percent who felt better in the IntraDose,
17 and it is exactly the same percentage of patients as in the
18 U.S. study and no patients had benefit in the placebo arm.

19 This is a pictorial representation of the FDA
20 palliative goal analysis. The green bars represent the
21 percentage of patients who felt better. The red bar
22 represents the percentage of patients who felt worse, and
23 the blue bar represents the percentage of patients who did
24 not have any change in their symptom score. In both
25 studies, the majority of the patients did not have any

1 | change in symptom score, and in both studies, particularly
2 | in the U.S. study, more patients got worse than feeling
3 | better in the IntraDose arm.

4 | In conclusion, regarding the primary efficacy
5 | endpoint of patient benefit, both studies failed to
6 | demonstrate clinical patient benefit of IntraDose versus
7 | placebo by both the sponsor's and FDA's analysis. Whether
8 | a change in score of 1 point is clinically meaningful needs
9 | to be discussed. If a 1-point change is excluded from
10 | counting as a benefit, then less than 5 percent of patients
11 | had any palliative benefit in both the studies. Even if a
12 | 1-point change is considered as a benefit, only 6 percent
13 | of the patients appeared to have any palliative benefit
14 | versus 25 percent who got worse in the U.S. study, and 19
15 | percent appeared to have benefit versus 22 percent who got
16 | worse in the Europe study.

17 | Furthermore, per the sponsor's analysis, only 5
18 | percent of IntraDose-treated patients obtained investigator
19 | and patient-specified primary treatment goals.

20 | The second major statistical issue is regarding
21 | association between objective tumor response and patient
22 | benefit in the IntraDose-treated patients. This is the
23 | sponsor analysis of the association between tumor response
24 | and patient benefit in the U.S. study. In this analysis,
25 | patient benefit includes both palliative and preventive

1 benefit. Note that only 10 of the 62, or 16 percent, had
2 both patient benefit and tumor response per this analysis.
3 The majority of the patients had neither benefit nor
4 response. This analysis does not provide a quantitative
5 measure of association such as a correlation coefficient in
6 the case of continuous variables. The p value is not
7 meaningful since the association is driven by nonresponders
8 and nonbenefitters.

9 A preferred measure of association is
10 sensitivity which gives the probability of a patient having
11 a benefit given that the patient has a tumor response. In
12 this analysis, the sensitivity was 48 percent; that is,
13 there is less than a 50 percent chance that a patient will
14 have benefit if the patient has tumor response.

15 This is the sponsor analysis of the association
16 between tumor response and patient benefit in the Europe
17 study in the IntraDose-treated patients. As in the
18 previous slide, in this analysis patient benefit includes
19 both palliative and preventive benefit. Note that only 6
20 of the 57, or 11 percent, had both patient benefit and
21 tumor response per this analysis. The majority of the
22 patients again had neither benefit nor response. The p
23 value again is not meaningful since the association is
24 driven by nonresponders and nonbenefitters.

25 In this study also the sensitivity was 43

1 percent; that is, there is less than a 50 percent chance
2 that a patient will have benefit if the patient has tumor
3 response.

4 This is the FDA analysis of the association
5 between tumor response and patient benefit in the U.S.
6 study in the IntraDose-treated patients. In this analysis
7 patient benefit includes only palliative benefit assessed
8 by the patient or investigator. Note that only 2 of the
9 51, or 4 percent, had both patient benefit and tumor
10 response per this analysis.

11 In this analysis the sensitivity was only 13
12 percent; that is, there is only a 13 percent chance that a
13 patient will have benefit if the patient has tumor
14 response.

15 This is the FDA analysis of the association
16 between tumor response and patient benefit in the Europe
17 study in the IntraDose-treated patients. Again, in this
18 analysis patient benefit includes only palliative benefit
19 assessed by the patient or investigator. Only 5 of the 54,
20 or 9 percent, had both patient benefit and tumor response
21 per this analysis.

22 In this analysis, the sensitivity was only 42
23 percent; that is, there is a 42 percent chance that a
24 patient will have benefit if the patient has tumor
25 response.

1 In conclusion, regarding association between
2 tumor response and patient benefit, the p values presented
3 by the sponsor are not interpretable, and the association
4 is weak and driven by a large number of patients classified
5 as nonresponders and nonbenefitters. There is less than a
6 50 percent chance that a patient will have benefit if he or
7 she has tumor response. In other words, tumor response
8 does not predict patient benefit.

9 In summary, both randomized studies failed to
10 demonstrate statistically significant clinical patient
11 benefit of IntraDose when compared to placebo. It is also
12 not evident that the objective tumor response translates
13 into clinical benefit.

14 Thank you.

15 DR. WILLIAMS: Thank you, Dr. Sridhara and Dr
16 Frykman.

17 My job is to summarize, and I'll try to be
18 merciful and brief.

19 To summarize, FDA found that there was a
20 reasonable rate of local tumor response. They found little
21 evidence of clinical benefit as defined by improvement and
22 prospectively defined palliative goals. This slide shows
23 the response rate of 32 percent and 22 percent on the
24 cisplatin gel arms and basically no responses, just 1 in
25 one trial, on placebo. So, it seems clear that the

1 | cisplatin gel causes some tumors to become smaller.

2 | These tables summarize the FDA's analysis of
3 | clinical benefit, as you've seen a couple of times. As
4 | you'll recall, the FDA analysis excludes preventive goals
5 | and includes palliative goals by either the investigator or
6 | the patient. In study 414, there is no suggestion of
7 | clinical benefit beyond what was shown by placebo.
8 | However, in study 514, if you just look at improvement or
9 | better, there appears to be some suggestion of more benefit
10 | on the cisplatin gel arm, but still at a fairly low rate of
11 | 19 percent versus 3 percent on placebo.

12 | However, as we've been discussing, there's a
13 | bothersome phenomenon noted in both analyses. In both
14 | studies, there's more worsening than improving of the
15 | primary endpoints in the cisplatin gel arm. In addition,
16 | there is more worsening than is noted in the placebo arm.
17 | And I think this would disturb me probably the most.

18 | As Dr. Sridhara noted, if you include worsening
19 | in statistical analyses and do a Wilcoxon rank sum test,
20 | there's no statistical significant between the arms and not
21 | even a trend.

22 | And finally, when palliative benefit was
23 | compared to objective tumor response, there was certainly
24 | no strong correlation found.

25 | So, the FDA presents these data and analyses to

1 | ODAC for assessment of whether cisplatin gel provides
2 | clinical benefit to patients with head and neck cancer,
3 | benefit that is greater than toxicity. When these studies
4 | were designed, the assumption of the FDA and the sponsor
5 | was that tumor responses do not necessarily equate with
6 | clinical benefit in the local treatment of head and neck
7 | cancer.

8 | Approval considerations were to be based
9 | primarily on prospectively defined palliative benefit.

10 | Questions for you to consider include whether a
11 | 1-point change on the 4-point palliative scale is
12 | meaningful within the context of this trial and, if so,
13 | whether the rate of benefit is acceptable in view of the
14 | toxicity of cisplatin gel.

15 | One needs also to seriously consider that more
16 | cisplatin gel patients showed worsening of their main
17 | problem than showed improvement. Certainly we've had some
18 | discussion of that and I'm sure we'll have more.

19 | Other issues that you may consider are the
20 | clinical meaning of the tumor responses in these trials
21 | considering the rate of the response, the nature and their
22 | duration, and the size of the tumors that are responding in
23 | view of the toxicity of treatment. In some settings,
24 | durable impressive responses have occasionally been
25 | supportive of approval. The sponsor has also collected

1 additional data on clinical benefit in more of an anecdotal
2 fashion.

3 Lastly, I want to address one issue that I
4 think is likely to come up in deliberations. An approach
5 to approval that we do not believe should be entertained is
6 accelerated approval. Accelerated approval allows for
7 approval based on a surrogate endpoint, such as response
8 rate, that is reasonably likely to predict clinical
9 benefit. After NDA approval, the sponsor must then do
10 controlled randomized trials to show clinical benefit.

11 However, in the case of cisplatin gel, the
12 randomized trials to evaluate clinical benefit have already
13 been done. In fact, the sponsor must be commended on
14 performing perhaps the only randomized, blinded trials in
15 head and neck cancer. If these trials have failed to
16 document clinical benefit, it seems doubtful that a later
17 trial, a phase IV trial, after accelerated approval would
18 succeed in doing so. Therefore, approval by the
19 accelerated approval mechanism does not seem to be a
20 reasonable option.

21 So, that concludes the FDA presentation. We'll
22 be glad to take questions from our seats.

23 DR. NERENSTONE: Why don't we have questions to
24 the FDA first. Dr. Lippman.

25 DR. LIPPMAN: Grant, I had a couple of

1 | questions to clarify some of the issues.

2 | In 1994, there was a meeting with the FDA which
3 | indicated there needed to be some sort of patient benefit
4 | information. What changed between that and the amendment?
5 | I don't know when patient benefit was put in during the
6 | trial, but what changed between what would have been a
7 | prespecified primary endpoint before the trial started to
8 | one of the things that I'm wrestling with and that's
9 | changing a primary endpoint during the trial?

10 | DR. WILLIAMS: The situation was that in 1994
11 | and 1995 we had meetings with the company. I was there.
12 | We recommended the concept of this kind of an endpoint, and
13 | clearly our intent was that there would be no approval
14 | unless we saw such a significant effect of the kind we were
15 | talking about. And whether you call that a primary or
16 | secondary endpoint really didn't matter to me and still
17 | doesn't matter to me. It's what's the p value for what we
18 | consider to be the most important analysis.

19 | We send comments to the company and the company
20 | do what they will do with it, and I guess they did not
21 | change the primary endpoint. Then later on statistical
22 | analysis is kind of -- maybe an amendment, probably the
23 | later amendment, would say, look, your primary analysis
24 | isn't addressing what we said it should be. We may not
25 | have expressed it as primary analysis before, but as our

1 | most important concern, and said that it should be co-
2 | primary.

3 | So, I don't think there's really been any
4 | difference of opinion. In fact, what I was hearing over
5 | the years I think from the company was more the fact that
6 | they didn't think they could get the patients to do it
7 | anyway, that the accrual was really a major problem and
8 | that was limiting them. So, I don't think there was really
9 | any change in our intent, and I think it's really more of a
10 | technical nature what we're hearing debated.

11 | DR. LIPPMAN: Well, I'm not so sure it's
12 | technical because whether it's a prespecified secondary or
13 | primary endpoint I don't feel as strongly about. But it
14 | does bother me that it changed in the middle of the trial.
15 | So, I just wondered what information was conveyed between
16 | FDA and the company to have them change in 1997 when, if
17 | the same information was relayed to them in 1994 -- but I
18 | agree with you about the issue of having co-primary
19 | endpoints. I don't know what that means really. One is
20 | used to base sample size and the other one could be a
21 | secondary. But I would have preferred prespecified, and so
22 | I was getting at why in 1997 and not in 1994.

23 | DR. NERENSTONE: Dr. Temple.

24 | DR. TEMPLE: Well, in this case, whether you
25 | think of the clinical endpoint as one to be carried out

1 | only if the response rate endpoint wins or whether you
2 | think of them as something where both have to win, it
3 | doesn't really affect the statistical analysis. We all
4 | agreed no correction was needed. And it's obvious the
5 | whole design of the study was intended, at least in part,
6 | to look at the clinical endpoint. That's why they did
7 | those scales and all those things. So, we think it was
8 | clear.

9 | But I still don't know the answer to my
10 | previous question. When, even after several years you
11 | finally figure out the importance of the clinical endpoint
12 | and you've calculated your sample size based on response
13 | rate, someone has to address the question of why you don't
14 | increase the study size because you have almost no chance.

15 | DR. LIPPMAN: Now, I have another question. I
16 | may have missed this during the presentation or in the
17 | book. But I thought, Grant, it was you who said that the
18 | primary endpoint of patient benefit, the co-primary
19 | endpoint, which was based on the algorithm -- is that
20 | correct -- in terms of the design, was a post hoc analysis.
21 | That didn't come through in the sponsor's presentation. I
22 | wanted to clarify that because, again, whether you design
23 | this up front in the trial or during the trial --
24 | obviously, ideally you'd like to have it up front -- but if
25 | the co-primary endpoint that we're talking about here,

1 patient benefit, was a post hoc analysis, which includes
2 really a primarily investigator-driven endpoint of
3 prevention, that to me is a more serious concern. So, I
4 just wanted to clarify that. Was it post hoc?

5 DR. WILLIAMS: Actually what is post hoc
6 depends on who's looking at it.

7 The FDA involvement can be very tight and close
8 or it can be a little more -- I don't want to say -- loose.
9 But I think in recent years we are much more involved at
10 every stage in making sure that everything we say is
11 addressed. We have more meetings, et cetera. In 1994 and
12 1995, we were doing some of that, but in general we give
13 advice and it's the responsibility of the sponsor to apply
14 it. The advice was given. The analysis plan was not even
15 formulated till later. So, it's hard to comment on an
16 analysis plan.

17 DR. LIPPMAN: What I meant by post hoc -- just
18 to clarify what I meant by post hoc, I meant that the study
19 is done, the data is there, and you start looking at it.
20 It's unblinded. You're looking at it. That's what I
21 consider a post hoc analysis, and I'm wondering if that was
22 what you meant when you said that the patient benefit
23 endpoint was a post hoc analysis.

24 DR. WILLIAMS: I didn't say that.

25 DR. SRIDHARA: Can I address your question?

1 | The data on clinical benefit was collected prospectively.
2 | The questionnaire was already there right from the
3 | beginning, and on every patient the data was collected.
4 | However, there was no hypothesis set up prior to the
5 | starting as to what should be the difference that we are
6 | looking for or how it's going to be analyzed or how even
7 | the patient assessment was going to be combined together.
8 | So, all those things were as the study was going on, our
9 | post hoc definition of what is a benefit or how do you
10 | define a benefit or how can you combine the patient and
11 | investigator assessment, et cetera.

12 | DR. LIPPMAN: So, when you said post hoc
13 | analysis, you meant the 1-point difference was not
14 | prespecified.

15 | DR. SRIDHARA: No. Neither the 1-point
16 | difference nor a hypothesis regarding patient benefit
17 | itself as to what is the difference that we are looking for
18 | was not defined at the start of the study. However, as I
19 | said, the benefit scores themselves or the treatment goals
20 | themselves were there right from the beginning and on every
21 | patient it was collected.

22 | DR. TEMPLE: Was the analysis planned before
23 | the study was unblinded or just in the course of the trial?
24 | Post hoc is not a fair term to use if everybody is still
25 | blind while they're doing it. Which do you mean?

1 DR. SRIDHARA: As the study was going on, all
2 this was evolving as the statistician commented on this.
3 Of course, I was not in the planning part. What we saw was
4 the final analysis plan which came that they were going to
5 use this patient algorithm.

6 I was trying to point out that this patient
7 algorithm -- I think even in our minutes we have recorded
8 that we didn't approve of combining the preventive and
9 palliative goals. And this was something that was defined
10 later on to combine the two goals together and also the
11 patient and investigator assessments together.

12 DR. LIPPMAN: Just to rephrase the question,
13 because one of the issues is the 1-point issue. That's one
14 of them that you asked us to address. Was this 1-point
15 issue prespecified before the study was unblinded?

16 DR. SRIDHARA: They had mentioned about it, but
17 we had expressed our concerns regarding whether it would be
18 meaningful or not. We were unsure.

19 DR. HOWELL: Madam Chairwoman, a point of
20 clarification?

21 DR. TEMPLE: The answer to your question is
22 yes, it was prespecified before they unblinded it. We just
23 said maybe we're not going to buy it. That's a different
24 question.

25 DR. LIPPMAN: No. That's different than post

1 | hoc, and I wanted to clarify that. So, it was not a post
2 | hoc analysis the way we would normally think of it.

3 | Then two other issues. You put up, Grant, as
4 | your two major concerns, concerns with blinding and
5 | concerns with internal consistency.

6 | Now, I raised the blinding issue particularly
7 | when you're talking about a 1-point change, all these
8 | things. So, I was concerned when I saw the different
9 | solutions. And I asked the sponsors about that, and they
10 | were confident that it still could be maintained.

11 | What leads you to believe -- maybe I missed it
12 | -- that that may not be the case, that the investigator may
13 | have some idea about what was being given?

14 | DR. FRYKMAN: First of all, it was very clear
15 | from the toxicity data that there was a difference between
16 | the placebo and the active drug. That's to be expected.
17 | For a single investigator who treats one patient, he may
18 | never be able to tell the difference, but for an
19 | investigator who may treat a half a dozen patients, he
20 | would ultimately acquire a sense of whether this was
21 | placebo or active drug. Ultimately, the drug would be
22 | unblinded.

23 | The second issue that came up was that in the
24 | adverse event database, we just incidentally happen to find
25 | a couple of things that suggested that there was a way to

1 | tell, and one of the issues was specifically a yellow-
2 | colored eschar. The only way that eschar could have become
3 | yellow-colored, at least in Europe, we were told by the
4 | applicant that there was a topical antibiotic that was
5 | used. That's not available here in the United States. So,
6 | at least the coloration of the eschar, just an incidental
7 | finding in the AE database, suggested that there was a
8 | color difference. How often that occurred, we don't know,
9 | but it appeared.

10 | The other issue had to do with local hair loss.
11 | We know that cisplatinum can cause this, and in fact you
12 | would not necessarily see hair loss with just injection of
13 | a collagen or saline into the local area.

14 | DR. LIPPMAN: Again, I'm not as concerned that
15 | there may have been toxicities that would lead someone to
16 | believe of what drug was there, but I am concerned if this
17 | lesion turned yellow and that's the color of the solution.
18 | Again, I don't know how great of a problem it was. The
19 | sponsors felt that this was not a big problem, and I just
20 | wanted to see if you feel that it was based on your comment
21 | about the blinding.

22 | DR. FRYKMAN: Yes. Again, I would get back to
23 | and reiterate the same comment that you made, that if this
24 | study had a very low level of noise, the curves were all
25 | smooth, and they appeared to respond, for example, the

1 | palliative benefit would definitely increase with the
2 | shrinking size of the tumor, and everything was all working
3 | together, then I'd frankly have a lot of faith in it.

4 | What happens in this case, though, is that
5 | we've got some data that's noisy, and on top of that, we've
6 | got some question about blinding. It's not clear to me
7 | that you're as able to detect or as sensitive -- the
8 | sensitivity to detecting a 1-point difference is the same
9 | when the trial is conducted impeccably, which is probably
10 | impossible, or close to impeccably as opposed to where it
11 | was not conducted impeccably, especially in the case of
12 | unblinding.

13 | DR. LIPPMAN: Do you have any idea how common
14 | it is for these lesions to turn yellow when they inject it?
15 | Is this a fairly common thing?

16 | DR. FRYKMAN: I don't know that. I don't know
17 | have a specific number. Again, it cropped up in the AE
18 | database. That wouldn't necessarily even need to be in
19 | there, but one of the investigators apparently put this in.
20 | I suspect it happened more often than was in the AE
21 | database because it wouldn't be something that you'd
22 | report. Did it happen 5 percent, 20 percent of the time?
23 | I'm not able to say.

24 | DR. NERENSTONE: Dr. Howell, could you briefly
25 | comment?

1 DR. HOWELL: Yes. Two points of clarification.

2 First, all the analyses were done on blinded
3 data before the blind of either study was broken.

4 Secondly, the sponsor has explained to the
5 agency that one investigator in Europe used a yellow-
6 colored antibiotic solution and painted that on the eschars
7 from that one study site. And that is the source of the
8 yellow in one study site from one investigator.

9 The color difference is not sufficient to be
10 able, once it is in the tissue, to cause any serious change
11 in color of the tissue under any circumstances.

12 DR. NERENSTONE: Other questions for FDA?

13 DR. LIPPMAN: Can I just follow up, Stacy?

14 You made a comment about internal consistency
15 and integrity of the data. That was a concern. Can you
16 elucidate why you had that concern?

17 DR. FRYKMAN: Yes, I can explain to you
18 briefly.

19 Again, we had an advantage in this trial in
20 that we had lots and lots and lots of data that was
21 collected over time on a visit-by-visit basis. Where I,
22 reviewing the data, had some trouble with, frankly,
23 sometimes believing what I was actually being told in a
24 specific patient was in the case where a tumor lesion would
25 shrink away completely. There are many cases, as you've

1 | seen in the data, in each study where a complete response
2 | was achieved. This is exciting and we hope something good
3 | comes out of it.

4 | The assumption, when the trial was designed,
5 | was that if a tumor shrunk away, that the problem
6 | associated with it, whether it was wound care, whether it
7 | was pain, whether it was obstruction, or whatever the case
8 | was, that that problem would also remit.

9 | What was frustrating is that it did not happen.
10 | There are cases where the tumor would remit completely and
11 | the patient's pain level would be identical. That's sort
12 | of one problem. There was a complete dissociation between
13 | tumor shrinking and a symptom going away.

14 | The other issue that I noticed was that on the
15 | occasion where the patient and the physician would choose
16 | the same endpoint -- it wasn't necessarily the primary one,
17 | but it was the same endpoint, such as pain control -- there
18 | would sometimes be a disparity between what the physician
19 | was saying -- he might rate it as a 3, and the patient
20 | might rate it as a 4. Well, again, a 1-point change you
21 | could argue really is important or that really is not that
22 | important. But when there's internal inconsistency between
23 | the same objective findings with regard to a patient, that
24 | was a bit troubling.

25 | The third factor has to do with the local

1 | toxicity. The sponsor, again, is to be congratulated on
2 | the absolutely superb job that was done by them and their
3 | investigators in collecting serial toxicity data. Keep in
4 | mind that there was no objective scale that the
5 | investigators had to go by, and they sort of winged it and
6 | said, well, this looks like a mild one, this looks like a
7 | moderate one, or this is gone completely.

8 | What happens in the case of a severe necrosis,
9 | for example, as opposed to no necrosis when the patient
10 | starts receiving the injections, what that does to wound
11 | care was somewhat of a question. One would expect that if
12 | there were severe necrosis that appeared after three
13 | injections, that local wound care, which had been rated as
14 | a 2 would get at least up to a 3. Again, you can look at
15 | the scale and decide if the scale was sensitive enough or
16 | not for that problem. But there was a disparity between
17 | what you'd expect to see with local wound care and what you
18 | actually saw rated by the patient and/or the physician.

19 | DR. NERENSTONE: Dr. Temple.

20 | DR. TEMPLE: It's worth noting the first of
21 | those concerns maybe, on further reflection, is not so much
22 | of a concern. The allegation would be that a tumor
23 | disappeared and the investigators were too stupid to
24 | attribute clinical benefit to that. Now, to the extent
25 | that's true, it undermines the results of the study and

1 makes them look weaker. I usually don't believe people
2 contrive to make their data look weaker. So, I don't
3 dispute the observation, but I'm not sure that comes under
4 the heading of bad behavior or something. That doesn't, I
5 have to say, seem like a major worry to me because it cuts
6 against the study.

7 I also want to observe that I think there are
8 many troubles with these data, but I want to distinguish
9 some of the ones that I don't think are.

10 The sensitivity argument does not seem
11 persuasive to me. We have no standard for what fraction of
12 people whose tumor shrinks ought to get a clinical benefit
13 out of that. There's no track record, no data. I think 50
14 percent would be pretty good if you believed all of them.
15 Now, you also heard we don't believe some of them, which is
16 a different question. But I don't think those are the main
17 problems.

18 I think the lack of persuasive findings might
19 be a real problem, but I think it's important to focus on
20 the ones that really are worrisome.

21 DR. NERENSTONE: If there are no further
22 questions for FDA -- Dr. Albain.

23 DR. ALBAIN: A few times it was mentioned that
24 you discounted some of the analyses of the sponsor because
25 the dropouts were greater in the placebo group, if I heard

1 | you correctly. To me, though, you'd expect that. If the
2 | agent is working, you are going to have patients go off
3 | study and they're going to progress much quicker on the
4 | placebo group.

5 | The sponsor had showed -- and I hadn't fully
6 | understood your analysis -- a rebuttal to your analysis
7 | earlier on, and I wondered if you can comment on that
8 | rebuttal explanation.

9 | DR. WILLIAMS: I think the only time when we
10 | really became insistent about the dropout issue is the
11 | preventive. It's not just dropout. It's the fact that
12 | there are no events to substantiate the difference between
13 | the two arms. It's all drop out by 28 or not drop out by
14 | day 28. The sponsor's analysis included as a failure
15 | someone who didn't make it to day 28. So, that's kind of
16 | like an event. You would think it would be driven by
17 | events you're trying to prevent rather than not making it
18 | to day 28. That's a case where the data are totally driven
19 | by differential dropout, and that's the case where we
20 | discounted those kind of data.

21 | DR. SRIDHARA: Can I add to that? Basically
22 | the duration of the clinical benefit had to be for 28 days,
23 | and if the placebo patients were there only for 28 days and
24 | they were removed from that study for palliative benefit,
25 | they were changed over or crossed over to the treatment arm

1 | because of progression of the tumor, not because of the
2 | clinical benefit, so they could not be assessed for
3 | clinical benefit beyond 28 days if they did not get beyond
4 | 28 days of treatment. The requirement was that they have
5 | to have 4 weeks of this benefit. So, they couldn't assess
6 | this.

7 | DR. TEMPLE: Could you just explain the
8 | prevention endpoint a little further? That's very crucial
9 | because we've just thrown out the major source of
10 | endpoints. So, if someone has gone 2 weeks on placebo and
11 | then progresses or something happens and haven't had the
12 | endpoint you're worried about preventing it, then the
13 | endpoint is never attributed to them.

14 | DR. SRIDHARA: Yes.

15 | DR. TEMPLE: Right? No.

16 | DR. WILLIAMS: That is the endpoint. They are
17 | given a negative endpoint for that. It's not that they're
18 | inevaluable. It's they have failed.

19 | DR. TEMPLE: So, they're said to have had the
20 | endpoint --

21 | DR. WILLIAMS: It's equally bad to do that as
22 | to go 3 weeks and then have it break through the skin.
23 | They're lumped together.

24 | DR. TEMPLE: So that when you actually count
25 | the events that you were trying to prevent, you don't see

1 | that difference. The whole thing is based on not making
2 | it.

3 | DR. WILLIAMS: In fact, it's the other way.
4 | It's worse on cis gel.

5 | DR. TEMPLE: Yes, that's what you said.

6 | DR. NERENSTONE: Dr. Rubinstein.

7 | DR. RUBINSTEIN: You argue that the preventive
8 | endpoint was invalid because of the difference in dropout,
9 | but the difference in dropout you demonstrated was
10 | primarily a result of earlier progression on the part of
11 | the placebo arm. It seems like that should have been
12 | anticipated at the beginning of the trial, and it also
13 | seems as if that could have been incorporated into the
14 | measurement of benefit. For example, one could even say
15 | that if a placebo patient is forced to drop out because of
16 | progression, that they didn't see the benefit by definition
17 | because they progressed. I'm not saying that that's the
18 | definition to use, but that certainly would be a
19 | possibility.

20 | It seems as if this issue wasn't addressed at
21 | the beginning and it seems like this is certainly related
22 | to potential benefit of the agent. You even said that in
23 | certain cases you would approve agents on the basis of
24 | reducing time to progression.

25 | DR. WILLIAMS: I agree with you that you would

1 | be showing something, and it basically would be early
2 | progression. But what were trying to do was a different
3 | type of clinical benefit or a different kind of endpoint.
4 | For showing clinical benefit according to patient symptoms
5 | or patient preference, this didn't fall within that
6 | category.

7 | Now, if you want to describe that as being for
8 | the discussion of should progression be acceptable for head
9 | and neck cancer, I would agree with you. But for saying
10 | should we lump this phenomenon, which is early progression
11 | of tumor, into these data that have to do with patient
12 | symptoms, then I don't think that that would be acceptable.

13 | DR. NERENSTONE: One of the questions I have
14 | just for clarification from a nonstatistical viewpoint, I'm
15 | not sure I have your same questions about the blinding
16 | because if you look at the placebo arm and the achievement
17 | of patient benefit according to the sponsor, there's a
18 | remarkably high benefit that they felt. In fact, it was on
19 | the placebo arm. In fact, isn't that one of the problems,
20 | that the study is so underpowered because there was such a
21 | big placebo benefit?

22 | I think that one of the things that we should
23 | take away from that is the importance of a placebo-
24 | controlled arm because I think if you look at the problems
25 | with the randomization and the unbalanced randomization,

1 | you could say that perhaps all of the effect is completely
2 | due to a placebo effect but randomization is the problem.

3 | DR. SRIDHARA: Yes. When you have imbalanced
4 | randomization, it is a problem. That's true. It was
5 | planned to be 2 to 1, and you see most of the benefits that
6 | you're talking about in the U.S. study which had 2.6 to 1.
7 | So, in fact, on the IntraDose there were even more
8 | patients.

9 | With respect to preventive benefit that we are
10 | talking about, in fact, of the 21 benefits that the sponsor
11 | has claimed in the U.S. study, 20 of them were preventive
12 | goals, and there was only 1 patient with palliative goal
13 | benefit. So, all these 20 patients got benefit from
14 | preventive goal, and when we don't have an incidence rate
15 | to compare what would be the baseline, we are talking of a
16 | very small time period. So, we don't know if nothing might
17 | happen during that period or not.

18 | The concern with the preventive goal is then
19 | that in fact we observed in 13 percent of the patients that
20 | an event happened, a failure happened, they had a breaking
21 | through or incidents of some of these adverse things that
22 | we were supposed to prevent happened; whereas, there were
23 | none in the placebo group. We are giving the benefit of
24 | doubt whether this was, in fact, because of the dropout
25 | rather than that we did not observe in placebo. In other

1 | words, we are saying that this is uninterpretable and
2 | therefore we can't use it.

3 | DR. NERENSTONE: Dr. Lippman.

4 | DR. LIPPMAN: A very quick clarification.

5 | When you focused on the dropouts, I think you
6 | pointed us to the top two figures, and one of them was
7 | patients who terminated for systemic progression, which I
8 | think was about 25 percent of the population. Can you
9 | clarify that? Because we knew a number of patients had
10 | systemic disease. It wasn't ineligibility criteria and
11 | it's not being adequately treated. You'd expect it to
12 | progress. So, when you say they were taken off for
13 | progression, is that really because they had symptomatic
14 | progression and needed to be treated, or just that the
15 | tumor grew greater than 25 percent, which you would expect
16 | with this kind of approach?

17 | DR. FRYKMAN: To be honest with you, I don't
18 | know the proportion of those. The way this table was
19 | derived was basically to go back through the database of
20 | what the sponsor had and sort of lump it into categories
21 | that seem to make sense. So, they didn't specify in that
22 | database, for example, whether the tumor had grown huge
23 | amounts or whatever the case was.

24 | I will say that my sense out of the protocol
25 | was, though, that systemic progression was noted usually on

1 | the basis of a substantially worsening KPS, substantially
2 | worsening weight loss, or the patient complaining about
3 | something. There wasn't continual serial monitoring by CT
4 | or specific physical exam to pick that up early. In fact,
5 | that was one of the concerns.

6 | It's debatable, but there was at least 1
7 | patient there where it appeared she kept receiving
8 | additional treatments with IntraDose. She was, I think,
9 | randomized to the active arm and kept receiving the gel and
10 | it kept her tumor small. You could slowly see her fall off
11 | KPS and weight-wise, and then down the line she was
12 | eventually declared to be, I think, systemic progressing.

13 | DR. NERENSTONE: If there are no more questions
14 | for FDA -- sorry. Dr. Rubinstein.

15 | DR. RUBINSTEIN: I don't understand why you say
16 | there was an imbalance in the randomization simply because
17 | the 2 to 1 ratio was not maintained exactly and, in fact,
18 | differed between the two groups. It wouldn't be uncommon
19 | for a targeted ratio not to be maintained exactly. That to
20 | me doesn't create an imbalance in the randomization.

21 | DR. SRIDHARA: It's only when we are trying to
22 | pool, but you have even lesser placebo and you are getting
23 | more patients from the U.S. study where they're claiming
24 | more responses, whether it is tumor response or benefit.
25 | If both were 2.6 to 1, then it was different. But one was

1 | 2.6 to 1 and the other was 1.5 to 1. So, that's where it's
2 | possible that it could cause imbalance.

3 | DR. TEMPLE: If there really is an
4 | international difference, then pooling them would
5 | exaggerate the study, since they had more of the patients
6 | getting treated.

7 | DR. SRIDHARA: Of course, it's evident that in
8 | the U.S. study, the preventive goal was picked at the
9 | primary goal more often than in the Europe study.

10 | DR. NERENSTONE: Dr. Blayney.

11 | DR. BLAYNEY: I'm trying to think where I'm
12 | wrong here. In spite of my concerns that this preparation
13 | is an elaborate way of giving epinephrine into a tumor and
14 | a low dose weekly cisplatin, no one disputes the fact that
15 | it shrinks tumors 25 to 30 percent of the time. And the
16 | statistical manipulations and machinations, rather, that
17 | you've done really revolve around an unverified pretty
18 | crummy instrument for trying to assess what's happening
19 | with symptoms in the head and neck. I think that's a very
20 | difficult area to assess symptoms. Getting people
21 | completely off of narcotics in 3 weeks is a big jump, and I
22 | think if an investigator says if didn't break through the
23 | skin or erode into the carotid artery or obstruct an
24 | airway, you sort of have to give the guy who's sitting
25 | there watching that happen or not happen the benefit of the

1 | doubt.

2 | DR. FRYKMAN: I guess about all I can comment
3 | on that is that is exactly what the thinking was when the
4 | agency and the applicant worked together to sort out
5 | exactly that question. This was a trial that was designed
6 | to help sort that out. The results are the results. But I
7 | think that goes to the core of exactly what the intentions
8 | were. And if you had polled a half a dozen people at that
9 | time, I think people would have said, yes, it makes sense.
10 | You got a problem. You make the tumor shrink. The problem
11 | should get better.

12 | DR. SRIDHARA: I just want to add regarding the
13 | analysis part itself. It is comparing to placebo and
14 | response rate, this is local response rate, this is not
15 | systemic response rate. I think you have to keep that in
16 | mind. We have already seen the survival graph that there's
17 | no difference between them. So, if the intention is to
18 | give some clinical benefit to the patient, then we are not
19 | seeing it in survival, so we ought to see it in some other
20 | clinical benefit. Even if we give all the preventive
21 | benefit that the sponsors are claiming, even by their own
22 | analysis, individually each study has not demonstrated a
23 | significant effect between placebo and the treatment arm.

24 | DR. BLAYNEY: And I guess I'd go back to the
25 | statement that the wrong -- I don't think we should

1 | penalize the sponsor for trying to mount a randomized
2 | controlled trial in this very difficult illness. We just
3 | don't have the tool and today you wouldn't design a study
4 | using this tool to get clinical benefit. And nobody in
5 | 1997 or 1994 was smart enough to come up with something
6 | that showed a clinical benefit other than it shrank tumors.

7 | DR. NERENSTONE: Mr. Gruett.

8 | MR. GRUETT: As a patient representative, most
9 | of my throat was removed. I was advised before the
10 | operation that I had a 15 percent greater chance of death
11 | through this procedure, but the quality of life thereafter
12 | would be wonderful. I elected to go with that option.

13 | Looking at the time to progression, if cancer
14 | would have come back in myself after 6 months, I had
15 | options of radiation and other things. But prior to the 6
16 | months, I had no option.

17 | Could this drug have given me the option
18 | increasing the time to progression to where additional help
19 | after that 6 month period I could have received radiation?
20 | If that's the case, it would have some value for someone
21 | like myself. I ask that. Dr. Frykman I think would be
22 | qualified.

23 | DR. FRYKMAN: Yes. I don't know that I'd be
24 | able to answer that. The sponsor may actually want to
25 | answer that some. But remember that the intent behind

1 | developing this therapy was to improve a single benefit in
2 | patients who could not have received other therapy. It's
3 | not intended to necessarily be a preventive modality in a
4 | case where there's not an identifiable and preventable
5 | problem. So, in your case, as I understand it, if you had
6 | recurred, again the other options would have been available
7 | to you, but this agent I don't think has ever been intended
8 | -- I don't think the sponsor intends it -- to be something
9 | that would be used to prevent a recurrence specifically.

10 | DR. NERENSTONE: Dr. Temple.

11 | DR. TEMPLE: I don't think we had going in a
12 | sure idea of what the best way to assess clinical benefit
13 | is. A lot of people in situations like this use visual
14 | analog scales, and you could have a visual analog scale for
15 | each of the symptoms too. Whether that would work better
16 | we don't know until somebody succeeds in showing something.
17 | The real test would be whether they prove useful when you
18 | actually find a drug that affects them.

19 | But whether that's the reason for any
20 | difference would be, I think, extremely hard to know. But
21 | it may be these steps were too far apart for anything to
22 | have a reasonable chance of making a big difference. That
23 | is possible because there weren't very many big
24 | differences. As people have been saying, the effect is, to
25 | the extent it was there, driven by the prevention claims,

1 | which you've heard a discussion of, and when you actually
2 | get down to the palliation score, the effect in each study
3 | can't be shown. But whether a visual analog scale would
4 | work better we don't know. We certainly wouldn't object to
5 | it. But in the absence of a success history, it's hard to
6 | know.

7 | DR. NERENSTONE: Dr. Glisson.

8 | DR. GLISSON: Yes. I was actually just going
9 | to make a comment on Dr. Blayney's comments, and then he
10 | sort of went round robin and said it himself.

11 | Just to help clarify this issue about
12 | preventive goals, I don't think they're unworthy, but the
13 | problem with the data as they stand is that you're unable
14 | to determine in the placebo arm what that baseline rate is
15 | of the event happening because there was such short follow-
16 | up in the placebo patients. We don't know, when we start
17 | out with somebody who's got a cervical mass near the
18 | carotid space, when they're going to have a carotid rupture
19 | or if they're going to have a carotid rupture. We might
20 | worry about it, but they might never have it before they
21 | die, or they might have it in 6 months because they live
22 | longer than we thought. So, it's just incredibly difficult
23 | without that data in the placebo group to know about the
24 | importance of these preventive endpoints.

25 | DR. NERENSTONE: Dr. Lippman.

1 DR. LIPPMAN: And also to pick up on one of Dr.
2 Blayney's other points is that I don't have any doubt in my
3 mind -- and I wouldn't think anyone here would -- that this
4 IntraDose is more active than placebo and it produces
5 responses. So, if that were the question, it would be an
6 easy one for me.

7 Obviously, the issue is the big word, "clinical
8 benefit," and that's where this all rides. Is that degree
9 of response, a 20 to 30 percent response, with a 2- to 3-
10 month response duration in the two trials, a benefit over
11 the toxicities and other issues?

12 Even the fact that it wasn't a validated tool
13 and you think it's crummy and we have better ones now,
14 which I'm sure you're right, I would feel better about
15 what's there if it was done up front and, even more than
16 that, if it was powered, if there was some way that each
17 study could actually have the power to look at it.

18 DR. NERENSTONE: Dr. Albain.

19 DR. ALBAIN: Grant, could you expand a little
20 more on why this could not qualify for accelerated approval
21 on response data alone?

22 DR. WILLIAMS: The point I made was that two
23 randomized, controlled clinical trials had been done to
24 look at clinical benefit, and depending on what you think,
25 let's say we didn't see it. That's usually what you do

1 after accelerated approval. So, if you're going to do
2 accelerated approval, first of all you have to have the
3 right population and basically have no other options, and
4 then you have to have some benefit that seems to be better
5 than what's out there. And then you have to be able to
6 design a trial that will show that it provides clinical
7 benefit. So, I think the latter point is the problem here.
8 If you've already done two trials and they didn't do it, is
9 it reasonable to think you're going to show clinical
10 benefit?

11 DR. ALBAIN: If we're all acknowledging that
12 the tool may not be what we would choose right now, if we
13 accept the response, can we not then go back to the sponsor
14 and request clinical benefit data post accelerated approval
15 that's designed a bit differently? I'm just asking.

16 DR. WILLIAMS: I think it's certainly something
17 that ODAC could discuss.

18 DR. TEMPLE: Grant is saying he's not sure it
19 meets the test for reasonably likely to predict clinical
20 benefit when you've had a trial that, even pooled, doesn't
21 really show that. But that's a judgment call. People
22 could disagree about that obviously.

23 DR. NERENSTONE: Dr. Lippman.

24 DR. LIPPMAN: Yes. Again, the issue of
25 accelerated approval. I never thought of this application

1 | in that context, but if you're asking do I think this is
2 | promising enough and is there room for another trial, given
3 | the issues we've talked about with the patient benefit, my
4 | answer would be yes.

5 | It's remarkable the two studies that were done
6 | actually. These are extremely difficult to do. There has
7 | been data from intra-arterial platinum for a long time
8 | that's more anecdotal that shows you can get responses in
9 | patients like this, but nothing that's been as well
10 | studied, randomized with all the bells and whistles. So,
11 | there has been a tremendous job and it's sort of being
12 | undermined by this patient benefit, which I'd like to see.

13 | So, although I don't think it's an accelerated
14 | approval issue, I don't think the issue has been resolved,
15 | and it would be nice to go on and do a larger study powered
16 | to look at the patient benefit, and I think it would be
17 | reviewed much differently here.

18 | DR. NERENSTONE: Maybe we should go on to an
19 | open conversation, if we've finished with questions with
20 | the FDA. Would anyone like to start the discussion? Dr.
21 | Glisson, did you have anything else you wanted to add?

22 | DR. GLISSON: I guess I'll just say from sort
23 | of a global perspective, I'm actually one of the strong
24 | advocates for looking at palliation in patients with
25 | recurrent head and neck cancer. It's one of the things I

1 | always talk about when I give a lecture on this subject.

2 | Unfortunately, what the sponsor of this trial
3 | has presented to us really just does not get at that issue.
4 | They've tried, but there are a number of issues that have
5 | been touched on by the committee, and I won't reiterate.
6 | For a lot of the reasons, we just fall short of the mark
7 | here in terms of showing that this is actually palliative.

8 | It does produce some responses. That's clear,
9 | but in fact, it's a tree we've cut down and we have a
10 | forest to worry about. It's an injectable technique when
11 | we know that, if it's not clinically evident, we have
12 | subclinical disease, microscopic disease, lots of other
13 | places besides the area that's being treated, and it's
14 | doomed to fail.

15 | I understand that it may be reasonable for a
16 | very small segment of the population of patients with
17 | recurrent disease where you really have nothing else to do
18 | and you're going to try to use it simply to reduce the
19 | possibility that they're going to have a horrible
20 | complication. But in fact, I think even that has not been
21 | shown.

22 | So, I'll say right out I'm a paid consultant to
23 | the FDA and I, of course, helped them come to many of their
24 | conclusions today. So, what they've presented is pretty
25 | much what I felt.

1 I'll agree with Dr. Lippman that there are
2 certainly some intriguing pieces of data here that would
3 suggest the therapy might have value, especially in concert
4 with systemic treatments.

5 DR. NERENSTONE: Dr. Couch had to leave early
6 but asked that I make her comments. She is a head and neck
7 surgeon.

8 She had serious concerns about this product.
9 She said that she felt that the sponsor's discussion about
10 who should not be eligible, in terms of affecting the
11 carotid with bleeds and actual blindness in patients with
12 the incidence of stroke, was unacceptably toxic and that
13 they really could not differentiate who might be eligible
14 and who should not be eligible. She felt that it's a drug
15 that she would not be able to use and she would not
16 recommend approval based on toxicity as well.

17 DR. PAZDUR: Could people discuss the concept
18 of a response rate with a local injectable disease versus a
19 response rate when we give systemic therapy? Because I
20 think that this is kind of mixing apples and oranges here.
21 Conventionally when we hear the term "response rate," we
22 think of response rates associated with systemic therapies
23 where you're eradicating, for example, micrometastases,
24 tumors all over the body. You have a systemic effect with
25 multiple tumors going down with lack of progression. It

1 | has a different concept to me than simply injecting
2 | something into a tumor that could be relatively small and
3 | in many cases surgery could handle this quite aptly in a
4 | very small surgical procedure in some cases.

5 | So, could people discuss this concept? Because
6 | it's one that is coming in other applications to us. To me
7 | there is a fundamental difference here which I can't get a
8 | handle on in my own mind, so to speak. So, I'd like some
9 | discussion on this point.

10 | DR. NERENSTONE: Dr. Redman.

11 | DR. REDMAN: Yes. I made this comment at lunch
12 | to some of my associates. It would be something to see
13 | radiation therapy brought before this group to claim
14 | clinical benefit. I might be shot by my dean when I go
15 | back.

16 | (Laughter.)

17 | DR. REDMAN: I think what is inherently wrong
18 | here is biologically something is happening. It's the
19 | tool, and I don't know what the right tool is. There is
20 | something going on. I don't know what global measure to
21 | use for a local effect other than it shrunk.

22 | Not all patients are going to have pain. The
23 | tool you used couldn't even predict those nonresponders.
24 | They all stayed stable with your tool, the vast majority of
25 | them. They didn't get worse with the tool. They didn't

1 | have more pain. They didn't have negative changes.

2 | So, I sort of agree with Dr. Pazdur. I don't
3 | know what tool to use for a local effect other than
4 | something shrunk. If you restrict yourself to everybody
5 | who's having symptoms from that one local site, you're
6 | never going to close your trial. It would just stay open
7 | continually. So, I'm somewhat conflicted. I think
8 | biologically something is going on here, some potential
9 | benefit. I just don't know, other than tumors shrinking,
10 | how to measure it. I just don't.

11 | DR. NERENSTONE: Dr. Lippman.

12 | DR. LIPPMAN: Rick, I think a lot of us, being
13 | medical oncologists, have a concern with local treatment of
14 | a systemic disease just at first. So, once you get beyond
15 | that, which you had to do for this, I think the idea of
16 | being able to palliate big tumors that are symptomatic --
17 | local failure is a huge problem in head and neck cancer.
18 | There's no question about it.

19 | Again, Dr. Glisson raised the issue of having
20 | good control rates to be able to analyze the positive
21 | benefit in a preventive way. And that's why I asked the
22 | issue about systemic failure because I would suspect
23 | systemic failure, and if someone is benefiting locally from
24 | a big tumor and it has a small nodule metastatic to the
25 | lung, I wouldn't abandon treatment on this program because

1 | you would expect it.

2 | I think you sort of answered the question in a
3 | sense when you said what does it mean when you have a 1.5
4 | centimeter tumor, which is I guess the stratum 1. It would
5 | be much more compelling if we saw this kind of thing in the
6 | big tumors because then you have more of a clinical problem
7 | that's easier to justify that you really are benefiting
8 | someone even though you know that they're going to fail
9 | systemically later. So, those are at least the issues that
10 | I think about in terms of a local treatment for this
11 | disease.

12 | DR. NERENSTONE: Dr. Sledge.

13 | DR. SLEDGE: I must say it doesn't bother me at
14 | all that you have an objective response in a small area
15 | when things are growing elsewhere.

16 | What does concern me is the agency's analysis
17 | that this wasn't a surrogate for anything, as far as we
18 | could tell. It wasn't a surrogate for any measurable
19 | clinical benefit. If there was some significant linkage
20 | between the two, I would find it an imminently reasonable
21 | endpoint. The problem is I don't see that in the analysis
22 | here.

23 | DR. NERENSTONE: Dr. Kelsen.

24 | DR. KELSEN: I agree with Bruce. The problem
25 | with this analysis that I'm wrestling with is the

1 | instrument to -- because the endpoint is palliation, but
2 | local control mechanisms are not limited to head and neck,
3 | as we all know. Radiofrequency ablation is used all the
4 | time for hepatic metastases in asymptomatic patients
5 | because they're small lesions. I think it is an issue for
6 | us to deal with in a real global way. It's, whatever the
7 | local treatment is, radiation included, how are we going to
8 | measure outcome, and I don't get a real sense today that we
9 | have a feel for that.

10 | DR. NERENSTONE: Dr. Blayney.

11 | DR. BLAYNEY: I would make the analogy to
12 | radiation to spinal lesions. They all hurt. You radiate
13 | them and after a while you can see healing with sclerosis,
14 | but very commonly people remain on narcotics. Occasionally
15 | some people will have paresis and you'll prevent
16 | progression to permanent paralysis.

17 | I think the issue here, analogous to this
18 | issue, there's a lot of dilution of the people who really
19 | need it. If this study was confined just to people with
20 | spinal cord compression, you'd see a lot greater clinical
21 | benefit. No question. Half of them or two-thirds would
22 | walk afterwards. Whereas, here maybe the 3 out of 100 or
23 | so that had spinal cord compression are the ones that had
24 | the dramatic clinical benefit and they're lost in the
25 | noise.

1 DR. NERENSTONE: Dr. Temple.

2 DR. TEMPLE: The thrust of Rick's question I
3 think was do you agree with basically what we've been
4 telling people, that if you're going to do a local therapy,
5 you really need to show that corresponds to some beneficial
6 outcome, that it shouldn't be presumed. There might be
7 some presumption about systemic responses, but here that
8 doesn't make sense.

9 What I'm hearing people say is that they
10 generally agree with that. Not that it's always easy to do
11 because sometimes what you think is caused by the tumor is
12 not really or whatever it is, and it proved difficult here
13 or maybe the instrument was no good, but that we should
14 keep pressing people to find an instrument or find a way or
15 select the right people so that when their tumors in fact
16 shrink, they feel better.

17 DR. PAZDUR: My feeling was is perhaps the
18 response rate is somewhat a proof of concept, that yes, you
19 can cause tumor shrinkage. But here again, there has to be
20 that leap to the clinical benefit issue of symptoms.
21 Especially if you're identifying these symptoms
22 prospectively as the most bothersome symptom, why aren't
23 you seeing an improvement and a correlation with tumor
24 reduction?

25 DR. NERENSTONE: I guess I'm going to play

1 | devil's advocate a little bit because I don't think that
2 | the instrument they used was so bad. I think that maybe
3 | the instrument they used was okay, and the whole concept
4 | may not be as active as they had wanted. So, I applaud
5 | them for using that, but not every trial is going to be
6 | positive, even if you have the right questions and you have
7 | the right instruments.

8 | Yes, they can come back and do it again, but I
9 | just think it may be a limitation of the drugs that are
10 | being tested.

11 | DR. PAZDUR: The other point that I wanted to
12 | get at is when we talk about a response rate of 30 percent
13 | for a systemic therapy, obviously we're feeling there are
14 | other tumors shrinking. Should we expect more from
15 | something that we're injecting right into the tumor? If we
16 | were taking a look at radiation therapy, for example, many
17 | times people get a very high complete response rate there.
18 | What is the magnitude of benefit that one would want from
19 | something that is being directly injected?

20 | DR. NERENSTONE: I think that might be a
21 | conversation that we shouldn't have at 6:30 today.

22 | (Laughter.)

23 | DR. PAZDUR: Agreed.

24 | DR. NERENSTONE: Dr. Lippman.

25 | DR. LIPPMAN: I can try to answer it.

1 (Laughter.)

2 DR. LIPPMAN: I don't have a flight to catch.

3 I think it depends on the population. We have
4 the world's expert in re-irradiation with chemotherapy in
5 Dr. Vokes here who can comment on that. I think if these
6 patients can't tolerate re-irradiation and radiation is no
7 longer an option, I think 30 percent in tumors that are
8 symptomatic is meaningful.

9 Again, I agree with Stacy on this. We have
10 better tools, but if this were powered differently, I think
11 these kind of differences might have been significant in
12 the individual studies and we'd be having a different
13 discussion. That's why I think another trial that's
14 powered may provide light.

15 DR. NERENSTONE: Dr. Carpenter.

16 DR. CARPENTER: If what I hear is true, I think
17 the one thing most everybody agrees on is if there's a
18 clinical benefit, you can't use this methodology to show
19 it. But it may be that if there's a clinical benefit, you
20 can't use this methodology equally well to show that it's
21 not there.

22 So, I think what we know is there's a small,
23 but definite response rate and that we don't know how to
24 get a clinical benefit or to measure it in this group of
25 people. Part of our problems have to do with the

1 methodology used, and part of our troubles have to do with
2 the lack of baseline knowledge about what to expect in this
3 clinical situation. Both are important.

4 I think we're going to end up coming down to
5 the line about a measurable benefit as far as shrinkage and
6 really just not knowing if there's, in fact, a clinical
7 benefit associated with this therapy given the information
8 we have now. And the decision is going to hinge on what do
9 we do with not knowing.

10 DR. NERENSTONE: Well, I think we're really
11 directed to the data that we have here. We're really sort
12 of limited.

13 I want to get to the questions. Two quick
14 questions, Dr. Albain.

15 DR. ALBAIN: I just wanted to go back, though,
16 if we are going to have a chance to consider the
17 accelerated question on response alone since there were co-
18 primary endpoints. You asked that we come back to it in
19 the discussion. To me, that's another way to look at what
20 we're all saying here.

21 DR. NERENSTONE: If we could turn our attention
22 to the questions.

23 DR. ALBAIN: Wait. I didn't get an answer to
24 my question.

25 DR. NERENSTONE: I'm sorry.

1 DR. ALBAIN: I asked if we are going to be able
2 to either write another question or have some discussion
3 about that. Rick?

4 DR. WILLIAMS: Why don't you finish these and
5 we'll see if you want to have another.

6 DR. ALBAIN: Okay.

7 DR. NERENSTONE: The first question. Do
8 1-point changes on the palliative scale developed by the
9 applicant represent significant clinical benefit within the
10 context of the clinical trials 414 and 514? And if so, do
11 the data in the charts presented from the primary
12 palliative goals represent significant evidence of clinical
13 benefit that outweighs the toxicity of treatment with the
14 cisplatin/epinephrine gel in patients with symptomatic
15 recurrent head and neck cancer?

16 People's comments specifically to this
17 question?

18 (No response.)

19 DR. NERENSTONE: Okay. Then we'll take a vote
20 on the first one. Does the 1-point change represent
21 significant clinical benefit? We have to go around the
22 table. Dr. Glisson?

23 DR. GLISSON: I'm not a voting member.

24 DR. NERENSTONE: Okay. Dr. Kelsen?

25 DR. KELSEN: No.

1 DR. NERENSTONE: I'm told you are a voting
2 member for this. You are allowed to pass and reconsider.

3 DR. GLISSON: I'm sorry. I was kind of
4 ignoring you because I didn't think I could vote.

5 DR. TEMPLE: This really asks whether the scale
6 they used is reasonable.

7 DR. GLISSON: I think the 1-point difference is
8 significant, as long as blindedness is maintained.

9 DR. NERENSTONE: So, that's a yes.

10 DR. KELSEN: No.

11 DR. ALBAIN: Yes.

12 MR. GRUETT: No.

13 DR. LIPPMAN: Yes, with the caveat that I know
14 nothing about these scales or what's valid or not. I
15 really would almost like to abstain. But my issue is more
16 concerned with what Dr. Glisson raised, the issue of a
17 control group and others, and less the 1-point issue.

18 DR. NERENSTONE: Is that a yes or a no or an
19 abstention?

20 DR. LIPPMAN: Yes.

21 DR. CARPENTER: No.

22 DR. PRZEPIORKA: Yes.

23 DR. NERENSTONE: Yes.

24 DR. SLEDGE: Yes

25 DR. PELUSI: Yes.