

1 | withdrew their consent because they didn't want to have the
2 | 3 times weekly injections.

3 | One has to appreciate that at the time of
4 | initiation of this trial, it was not clear to the patients
5 | what their potential benefit of this therapy would be, and
6 | therefore the threshold, at least that was the risk a
7 | priori -- the threshold for withdrawal from the trial would
8 | be low. That has not materialized, fortunately, because
9 | withdrawal in total -- and I'll get back to that later --
10 | was not considerable.

11 | A little bit about demographics. As I said
12 | before, stratification by center was done, but not by the
13 | more relevant risk factors. However, with this number of
14 | patients, 499, it balanced out beautifully. Differences
15 | were very small. There was no statistical difference, for
16 | example, for the more powerful of the risk categories that
17 | we have used, which is Breslow thickness.

18 | Further to Dr. Buzaid's presentation, you see
19 | here the categories of Breslow tumor thickness. Our
20 | patients in this stage II melanoma patient population
21 | consisted of patients with tumor thickness of 1.5
22 | millimeters and more. This should be looked at in
23 | categories and not as a continuous variable because,
24 | obviously, these subcategories follow in some ways
25 | anatomical boundaries.

1 This is one of the busiest slides that I'm
2 going to show this afternoon, and it will take me some time
3 to guide you through it, but this is quite a crucial slide
4 for the message of the presentation.

5 This is the long-term analysis on eligible
6 patients for disease-free interval, and disease-free
7 interval, the time from initiation of therapy to relapse,
8 the difference remains significant. This analysis was done
9 when a median time to follow-up existed of 4.4 years. That
10 means that the first patients were up to 7 years in the
11 trial and the last patient entered 36 months.

12 The time to 25 percent relapse -- and I do not
13 show that on the slide here -- was 1.3 years in the
14 observation arm and 2.1 years in the Roferon arm, a rather
15 remarkable reduction of 25 percent, or 10 months.

16 The p value for the Kaplan-Meier estimates, as
17 you see here, is .035.

18 The number of relapses in the Roferon arm in
19 total was 100; in the observation arm, 119; a difference of
20 19.

21 Last but not least -- and that is perfectly
22 justified by the protocol -- if one would do a cutoff
23 analysis, something that most simple people like myself
24 would understand better, if one would do a cutoff at 3
25 years, then the percentage of withdrawals here would be 32

1 | percent and 49 percent in the observation arm, a difference
2 | of 17 percent. With stratification by center, that carries
3 | a p value of .005.

4 | Breslow thickness, as presented before by Dr.
5 | Buzaid, is a powerful risk parameter or prognostic factor.
6 | We show this slide here today of the Kaplan-Meier estimates
7 | for the specific subsets of Breslow thickness only to show
8 | that the impact, the effect, for all categories is similar.

9 | I also need to inform you that there was no
10 | interaction between this risk parameter and the outcome as
11 | disease-free interval, nor was there any interaction
12 | between age and sex and this outcome parameter.

13 | Before I start explaining this slide, it's my
14 | task to bring across to you that this study was never
15 | designed to evaluate overall survival. I'll try and
16 | explain that.

17 | A sequential analysis was performed and a
18 | triangular design was used. That means that
19 | discontinuation of recruitment into the trial was done at
20 | the moment in time that there were enough events to answer
21 | the question about disease-free interval. By nature of
22 | things, there will always be more events such as relapses
23 | than death. Therefore, it is a little bit unreasonable to
24 | expect that one would be able to show a difference for an
25 | outcome parameter which has less events like death.

1 As it happens, we come close with a p value of
2 .059. But the only thing we can conclude from that is that
3 there is a strong trend.

4 However, as I said before, there is a robust
5 correlation between disease-free interval and overall
6 survival, and I will get back to that when I conclude this
7 talk.

8 There were 59 deaths in the Roferon arm in this
9 analysis and 76 deaths in the observation arm. It's
10 obvious that at 6 years, at the tail end of the curve, like
11 with the other curve, there are few patients in the
12 analysis simply because median follow-up time here as well
13 was 4.4 years.

14 Dr. Buzaid showed a slide in his presentation
15 where he put together disease-free interval or time to
16 relapse and overall survival. Sorry. This is disease-free
17 interval obviously for both and here is overall survival.

18 I would like to show to you what the difference
19 is between the two with regard to events. 100 relapses in
20 the Roferon arm, 119 in the observation arm. 59 deaths in
21 the Roferon arm, 76 in the observation arm. One difference
22 of 19. One difference of 17.

23 I think that the crux of my argument for this
24 afternoon is that if we manage to delay or prevent
25 recurrence in this disease, it is possible that we may

1 | delay death as an event. I think that that is an important
2 | thing to keep in mind.

3 | The shapes of these curves are similar, but
4 | that's the only thing I can say about them.

5 | It's very important for a regimen that has to
6 | be continued for 18 months that tolerability is more than
7 | acceptable. We have looked at the adverse event pattern of
8 | this dose used in this study, 3 million units 3 times a
9 | week, and we have concluded that the pattern of adverse
10 | events that we observed is not different from the pattern
11 | of adverse events that we see with the use of this drug in
12 | other indications.

13 | There are no surprises and there are no events
14 | that suggest the sort of toxicity that one would relate to
15 | a higher dose of this drug that we have also seen in other
16 | studies with our drug in the past.

17 | So, here you see the percentages of the
18 | patients with flu-like symptoms, asthenia, headache,
19 | nausea/vomiting, depression, and dizziness being the most
20 | commonly reported adverse events in this trial.

21 | If we then look at the percentage of patients
22 | with grade 3-4 toxicity, then these percentages are low.
23 | Again, this is a well-established safety profile that we
24 | know and have seen several times before with the use of
25 | this drug.

1 What is important to show, however, is that
2 there is a certain withdrawal rate, and this withdrawal
3 rate is 14 percent. 35 patients withdrew from treatment
4 over the course of 18 months. The majority of these
5 withdrawals happened around the 1-year time point. More
6 importantly, they were for events such as asthenia, flu-
7 like symptoms, dizziness, depression, usually grade 1-2.
8 There were 9 patients, though, with grade 3-4 that
9 withdrew, and you see them described here. There were 2
10 patients withdrawn for severe increases in liver enzymes.

11 I will now move on to discuss the study that
12 formed the supportive data for this application, the study
13 performed by the Austrian Melanoma Group. Recruitment took
14 place between 1990 and 1994, roughly in parallel with the
15 French study. This was also a prospective, randomized,
16 multi-center trial. Patients had Breslow tumor thickness
17 of 1.5 millimeters and more, in other words, clinically
18 node-negative patients, exactly the same patient population
19 as we had in the other study.

20 The primary efficacy parameter was also the
21 same, disease-free interval, time from initiation of
22 therapy to relapse.

23 The dose was the same, the regimen slightly
24 different, and the treatment duration was different. 3
25 million units were given 5 times weekly, once daily for 5

1 days, for a duration of 3 weeks, sort of an induction
2 regimen. The maintenance part was, however, the same as I
3 described for the previous trial.

4 I base this part of the presentation on the
5 publication database. The data that I've presented and
6 present from the publication, this publication has a
7 patient number of 311: 154 in the Roferon arm, 157 in the
8 observation arm. There is currently a database that has
9 330 patients, as 19 CRFs were collected after the
10 publication cutoff.

11 Demographics. Again, I show Breslow thickness
12 as a risk parameter only, and here as well, whereas there
13 was no stratification for this parameter, both arms are
14 well balanced. There is certainly no statistically
15 significant difference between the two. There are only
16 small differences that are not clinically relevant.

17 These are the Kaplan-Meier estimates for this
18 study, also for disease-free interval. Here you see the
19 observation arm. Here you see the Roferon arm.

20 This analysis was done in September 1995 when
21 patients had been in the study for at least 1 year and
22 observed and followed up for at least 1 year. So,
23 recruitment took 3 years, 154 here and 157 on the other
24 side.

25 37 patients relapsed in the Roferon arm, 57 in

1 | the observation arm. The p value was less than .05.

2 | Here you see our overall conclusions. We have
3 | seen parallel efficacy in two independent studies with 800
4 | and more patients in these studies all together.

5 | The reduction in recurrence rates or time to
6 | recurrence of 25 percent in our view is clinically
7 | meaningful. This translates into prolongation of disease-
8 | free interval of 9 to 10 months. The time to 25 percent
9 | relapse in the French study, in the pivotal study, was 1.3
10 | years in the observation arm and 2.1 years in the Roferon
11 | arm. If we cut off at 3 years, 32 percent of patients have
12 | relapsed in the Roferon arm and 44 percent in the
13 | observation arm.

14 | We have seen a strong trend towards increase in
15 | overall survival that is properly correlated with the
16 | increase we have seen that is statistically significant for
17 | disease-free interval.

18 | This drug has a well established safety
19 | profile. The withdrawal rate over 18 months in this study
20 | was low. It was 14 percent, but in view of the fact that
21 | patients did not know exactly what their advantage was
22 | going to be, this was very reasonable. The drug was
23 | therefore well tolerated. Patients could continue with
24 | work and lead an essentially normal life. This is
25 | important for a prophylaxis regimen and a regimen that

1 | relies on compliance and has to be maintained for 18
2 | months.

3 | We designed low dose Roferon-A for a situation
4 | whereby there's a low tumor burden and an intermediate to
5 | high risk of recurrence. What this therapy does is it may
6 | prevent or delay the dreadful moment of disease recurrence.
7 | It may, therefore, delay death as visceral metastases
8 | directly lead to death within 12 to 18 months.

9 | We, therefore, recommend low dose interferon
10 | alpha 2a, otherwise called Roferon-A, therapy as adjuvant
11 | therapy of stage II melanoma patients. These are patients
12 | with clinically node-negative melanoma. This translates
13 | into a Breslow tumor thickness of more than 1.5
14 | millimeters. We recommend a treatment duration of 18
15 | months.

16 | This brings me to the end of my presentation.
17 | Thank you.

18 | DR. SCHILSKY: Thank you very much.

19 | Are there questions from the committee members
20 | for the sponsor? Dr. Raghavan?

21 | DR. RAGHAVAN: These are two quite large sets
22 | of data and you're asking us to accept disease-free
23 | interval as a good surrogate of overall survival.

24 | The one thing that troubles me and puzzles me
25 | is the time of recruitment to these two trials was for the

1 French trial January 1990 to December 1993, and the
2 Austrian trial sometime in 1990 to 1994. By my
3 calculations, you should have follow-up data conservatively
4 to 9 years and maybe to 10 years, and yet the survival
5 curves that you present show weak power out at 6 years.
6 So, effectively you're presenting old data that haven't
7 been updated and yet asking us to accept disease-free
8 survival rather than overall survival. Could you clarify
9 why that is?

10 DR. HOOFTMAN: I would not immediately agree
11 with that. With this proposal for this therapy in an
12 indication of stage II melanoma, median time to death is 7
13 to 8 years. Our median follow-up is 4.4 years. We are,
14 however, getting closer to the moment in time where we
15 could produce longer follow-up data.

16 DR. RAGHAVAN: No. I'm sorry. I guess I asked
17 the question without clarity and I apologize.

18 I understand what you just said, but the
19 reality of the situation is that even your disease-free
20 survival curves, unless I'm misinterpreting them, don't go
21 out to the full time that would be eligible for the
22 duration of follow up. It looks to me like the data that
23 you've shown us, whether they're disease-free or total
24 survival, are old data. I can't understand if you had
25 patients entered in 1990 who you propose are still alive,

1 | which I hope is the case, why the survival curves have so
2 | few cases at 6 years that are still going. It doesn't make
3 | sense to me.

4 | Why have you censored at 6 years? Why do the
5 | curves not go out at least to the 9-year point?

6 | DR. SCHILSKY: Would you please identify
7 | yourself?

8 | DR. WASSNER: I'm Elizabeth Wassner. I'm
9 | working in oncology in Basel.

10 | The dossier has been submitted two years ago.
11 | These are the data that you reviewed.

12 | Now, if we look at 5-year survival data, which
13 | is actually a reliable time point in the study, we've got a
14 | p value of 0.021, which is even more significant than what
15 | we've presented here.

16 | DR. SCHILSKY: Can we just clarify that perhaps
17 | by hearing a brief summary of the registration history?
18 | You just said that the materials were submitted two years
19 | ago and that that's the data that we're reviewing today.

20 | DR. WASSNER: Yes.

21 | DR. SCHILSKY: Since you originally submitted
22 | the data two years ago, have you provided any update to
23 | those data?

24 | DR. WASSNER: We haven't been requested to do
25 | that, but it is planned, of course, to look longer into

1 | these data. But right now this is the data we have, and
2 | we're actually claiming overall disease-free survival and
3 | this is, I think, mature data. Overall survival, of
4 | course, would request 10-year follow-up in this population,
5 | and an end of recruitment, which is December 1993. 10-year
6 | data are still far away.

7 | MS. da SILVA: Just to clarify the regulatory
8 | history of the submission, we originally submitted our
9 | application of September 1997 and the year time clock for
10 | acting on that with FDA was in September of 1998 when we
11 | received questions and responses from them. We then took
12 | into account their comments and resubmitted a response in
13 | March of 1999, which included a second study with the
14 | Austrian publication, and then we are here before you
15 | today, of course. We were notified in July, so we have not
16 | submitted an update as of yet.

17 | DR. SCHILSKY: Thank you.

18 | Other questions? Dr. Nerenstone.

19 | DR. NERENSTONE: I'm not familiar at all with
20 | these clinical trials groups. We're usually given a little
21 | bit more information about frequency of follow-up or how
22 | patients are clinically staged. That's sort of important
23 | in a study where it's a disease-free interval difference
24 | that you're looking at. Can you tell me how often these
25 | patients are followed and what kind of tests are done,

1 | whether liver function tests are done, CT scans, or
2 | clinical, and how often that interval is?

3 | DR. HOOFTMAN: Can I please defer this question
4 | to Professor Grob who was the lead investigator of this
5 | trial?

6 | PROFESSOR GROB: Jean-Jock Grob, dermatology,
7 | France.

8 | Both groups were followed exactly in the same
9 | way. People were examined every 3 months and they
10 | underwent CT scan and x-ray explorations every 6 months,
11 | exactly in the same way in the two groups.

12 | DR. NERENSTONE: And were laboratory
13 | evaluations done as well at every 3-month follow-up?

14 | PROFESSOR GROB: Yes.

15 | DR. NERENSTONE: Were CNS relapses considered
16 | relapse?

17 | PROFESSOR GROB: Yes.

18 | DR. SCHILSKY: Could I just pursue that before
19 | you sit down? Because, as I understand it, the follow-up
20 | was done for 36 months according to the protocol, and then
21 | there was an effort made I guess by the company to then
22 | ascertain again the clinical status of all the patients
23 | sometime after the protocol-prescribed follow-up was
24 | completed.

25 | So, can you tell us something about what the

1 follow-up of the patients was in that interval of time from
2 when the protocol-specified follow-up ended until the data
3 were collected again from all the participating sites? Did
4 the investigators continue to follow the patients on the
5 same schedule? Do we have a way of verifying in fact that
6 they were followed on the same schedule with the same tests
7 being done at the same intervals on both arms?

8 PROFESSOR GROB: Well, I would say that we were
9 out of the limits of the protocol, but most patients were
10 followed exactly in the same way and some were followed
11 more closely because the follow-up protocol is a little bit
12 less tight than the usual process in France. The only way
13 to check it would be to come back to the files because a
14 point was made after.

15 DR. SCHILSKY: Yes. It is a bit of a concern
16 because the ascertainment of relapse status in a sense
17 could be very unbalanced in that interval of time when the
18 protocol was no longer necessarily being followed. Since
19 that's the primary endpoint that we're looking at here, I
20 think we have some concern about whether in fact patients
21 were followed exactly in the same way. It was an unblinded
22 study. There could have been biases in favor or against
23 the treatment that were in the minds of the physicians or
24 the patients.

25 Okay. Other questions from the committee? Dr.

1 Johnson?

2 DR. JOHNSON: I think I read and understood Dr.
3 Hooftman's presentation to say that the pivotal trial was
4 designed without consideration of the usual prognostic
5 factors being used for stratification purposes. I believe
6 that was correct. Is that correct?

7 DR. HOOFTMAN: I wouldn't say without
8 consideration, but there was no stratification for the more
9 powerful risk categories such as Breslow, nor for age or
10 sex. However, as I showed you on the slide, there was no
11 imbalance between the two.

12 DR. JOHNSON: I won't be too melodramatic, but
13 I'm very surprised that a study of this size undertaken at
14 the time that this was would have done that, to be honest.
15 I'm just very surprised. This is not new information
16 really. I just don't understand why a trial of this size
17 would be undertaken without proper consideration of known
18 prognostic factors.

19 What you showed us was a Breslow depth. You
20 haven't shown us the other prognostic factors I don't
21 believe.

22 DR. HOOFTMAN: Can we call up these? We have
23 some backup slides, with permission.

24 I can already start and answer the question.
25 There was no imbalance at all with regard to the risk

1 categories of Breslow tumor thickness, age, sex, location
2 of primary or pathology.

3 DR. JOHNSON: Do you have location?

4 DR. HOOFTMAN: Here you see depicted the sites
5 of melanoma or location of primary.

6 DR. SCHILSKY: Anything else you want to see,
7 David?

8 DR. JOHNSON: Yes. Well, I want to ask a
9 couple of other questions.

10 You gave us the overall survival data and you
11 mentioned the number of deaths, but I don't recall. Were
12 all of those deaths due to melanoma?

13 DR. HOOFTMAN: No, they were not all due to
14 melanoma.

15 DR. JOHNSON: Can you give us the causes of
16 death on the two arms?

17 DR. HOOFTMAN: 4 deaths were not related to
18 melanoma, 2 in each arm.

19 DR. JOHNSON: The other question I have, I was
20 also surprised at the differences in the number of patients
21 not eligible on the treatment arm. I believe there were 9
22 patients, if I'm not mistaken, versus 1 on the observation
23 arm.

24 DR. HOOFTMAN: That's correct.

25 DR. JOHNSON: The skeptic that I tend to be, if

1 | all 9 of those patients had, in fact, progressed, what
2 | would that have done to your DFI curves and the observation
3 | arm had remained the same? Would it still be statistically
4 | significantly different?

5 | DR. HOOFTMAN: That is a perfectly reasonable
6 | question.

7 | DR. JOHNSON: I thought so.

8 | (Laughter.)

9 | DR. HOOFTMAN: Can I defer this to my
10 | colleague, Sam Givens, the statistical expert?

11 | DR. GIVENS: My name is Dr. Sam Givens. I'm a
12 | statistician at Hoffmann-La Roche.

13 | Yes, that is a good question. Let me start off
14 | by answering it in one way, and that is that the sequential
15 | analysis that was done, which was defined in the protocol
16 | as the primary analysis to stop recruitment of the trial,
17 | was done on all patients. There were no exclusions in that
18 | analysis and that analysis was significant at the .038
19 | level.

20 | I think they naively did not include Breslow in
21 | their anticipated statistical analysis for that sequential
22 | stop. Their thought was that if they're balanced, they'll
23 | be okay, and the other aspect was, when we followed the
24 | patients longer, the expectation was to include that
25 | category into the final analysis.

1 As to the question of if all 9 of those
2 patients had died, I believe that reduces the difference in
3 survival by 9 and would drop it from 19 to 10. My
4 expectation is certainly that that would have lost
5 significance.

6 DR. JOHNSON: I'm asking also DFI. This is
7 overall survival. I'm asking for DFI as well, which is the
8 only endpoint that you showed a statistically significant
9 difference.

10 DR. GIVENS: So, now you're saying in the
11 hypothetical situation on DFI, if we had known all 9 of
12 those patients had had a relapse.

13 DR. JOHNSON: Correct.

14 DR. GIVENS: Well, those 9 patients were
15 included in the analysis with what we knew about them, but
16 I think that had all 9 of those died that -- or had all 9
17 of those relapsed, I would anticipate that they would not
18 be significant.

19 DR. SCHILSKY: Dr. Lippman.

20 DR. LIPPMAN: Actually I had a comment and a
21 question, but before that, just following up on the last
22 point, all 9 patients were included in an intent-to-treat
23 analysis that was presented in terms of disease-free and
24 overall survival?

25 DR. GIVENS: The sequential analysis that was

1 | done included all patients. There were no patients who had
2 | been eliminated at that time that led to the stopping of
3 | the trial -- stopping of recruitment. Sorry.

4 | DR. LIPPMAN: So, I think that answers that
5 | question, Dave, if they were included.

6 | DR. JOHNSON: Well, actually I don't think
7 | that's what I heard. What I heard is that those 9 were not
8 | included in that analysis. Maybe in the stopping of the
9 | trial but not in the analysis of the DFI.

10 | DR. SIMON: If I could clarify what I heard, it
11 | sounded like they were included at the interim analysis
12 | that led to the stopping of recruitment, but they were
13 | excluded in the analysis based on further follow-up.

14 | DR. JOHNSON: That's right. That's what I
15 | understood, and the numbers reflect that I think there.

16 | DR. GIVENS: You are both correct with that
17 | statement.

18 | DR. SIEGEL: Can I get a clarification? Dr.
19 | Simon just referred to the analysis that led to the
20 | stopping of the trial as an interim analysis. If I
21 | understood the presentation, that's the analysis you
22 | presented as the primary analysis with the .038. This
23 | analysis is the analysis when everybody had 3 years of
24 | follow-up, which you presented as a secondary analysis, and
25 | then additional follow-up beyond 3-year data -- you haven't

1 | presented those data. Is that a correct understanding?

2 | DR. HOOFTMAN: It's almost correct. The
3 | primary efficacy analysis was for disease-free interval.
4 | It was at the same time the analysis that determined the
5 | discontinuation of recruitment in the trial. You have to
6 | set that apart from the long-term analysis that is an
7 | exploratory type of analysis.

8 | The third analysis was solely -- it was done
9 | retrospectively, but to get more information with regard to
10 | overall survival. The trial and the protocol as such was
11 | written for a 36-month course. That means that the last
12 | patient entered reached 36 months and then the long-term
13 | analysis was performed.

14 | DR. SCHILSKY: Dr. Lippman.

15 | DR. LIPPMAN: I just have to clarify one other
16 | thing. Maybe I'm just missing the point. Hypothetically
17 | we assume what happened if they all progressed, and that's
18 | a big concern when they're eliminated from an intent-to-
19 | treat analysis. But we don't have to be hypothetical here.
20 | Right? You have follow-up on those and they were included
21 | in your analysis? We know as much as we know about those
22 | patients?

23 | DR. HOOFTMAN: These are the patients that were
24 | excluded from this long-term type of analysis. 5 of these
25 | patients never received an injection because they, so to

1 say, got cold feet and they didn't want to be in the study
2 once it was clear what was going to happen. 3 patients had
3 the wrong diagnosis. The patients that you see at the top
4 of the list had stage IV and died after a few days. The
5 second patient had a Clark level I tumor. The third
6 patient had lymphoma. The fourth patient had a previous
7 melanoma, which was also an exclusion criteria, and the 1
8 patient in the observation arm had a previous melanoma.

9 DR. LIPPMAN: So that that would add 3
10 relapses, if they were included in patients that had the
11 right eligibility criteria.

12 DR. JOHNSON: Well, no. I would say 5 at a
13 minimum, the 5 who withdrew their consent. To me that's
14 not an intent-to-treat analysis. That's a "I took out 5
15 people I didn't want to include" analysis.

16 DR. LIPPMAN: The question that I had actually
17 is this issue of disease-free interval and the importance
18 of that. Actually in the context of everything that we've
19 heard this afternoon, the first presentation by Dr.
20 Kirkwood and this, I actually was very disturbed by the
21 finding of 1690 and the explanations for that in which you
22 saw significant improvements in disease-free but absolutely
23 nothing, not even a trend in survival. In this case
24 there's a significant effect in disease-free survival and a
25 .056 which translate to 59 deaths, if I read the slide

1 | correctly, in Roferon, and 76 in the observation arm. So,
2 | it's certainly consistent and in the right direction.

3 | But I want to get to the explanation that was
4 | given by Dr. Kirkwood, at least that I asked earlier, that
5 | the major aspect of that difference in survival he thought
6 | could have been explained by salvage interferon. So, the
7 | question here, have you looked at patients? Two issues.
8 | One, on the observation arm, if there as a drop-in rate on
9 | the interferon. Certainly it has been available and people
10 | have been talking about interferon and melanoma for a long
11 | time. And two, at relapse, the differences between the
12 | arms in terms of salvage interferon.

13 | DR. HOOFTMAN: Would you please repeat the
14 | question?

15 | DR. LIPPMAN: So, the question is, on the
16 | observation arm, of the patients that recurred, what was
17 | the salvage therapy? Were a substantial number of the
18 | recurrences on the observation arm treated with interferon
19 | at recurrence?

20 | DR. HOOFTMAN: The only thing I can do in this
21 | situation is ask Professor Grob to answer the question. I
22 | think that the difference with what Dr. Kirkwood's group
23 | has done is that we have not formally retrieved that
24 | information in a retrospective fashion.

25 | PROFESSOR GROB: If I understood you well, the

1 question is what kind of therapy did the patient receive
2 after relapse. We do not have this information in our
3 data. Of course, we can go to the files, but I think
4 really that none of the therapy of metastatic disease, of
5 distant metastatic disease, visceral metastases has shown
6 any effect on the overall survival. So, this is my first
7 answer.

8 And the second would be that it is highly
9 likely that the treatment after recurrence were well
10 balanced between the two groups. But the effect of the
11 treatment on the overall survival, I would be happy to get
12 one.

13 DR. LIPPMAN: The reason I bring that is up is
14 I was surprised also by the presentation of Dr. Kirkwood
15 that there as a major difference between the arms in terms
16 of who had gotten interferon, and that that was the best
17 explanation at least that exists, as I understand, for the
18 fact that you see an improvement in disease-free survival
19 but nothing in terms of survival. If that was even a
20 potential confounder in this study, that might account for
21 why your p value is .056 instead of .049. Could that have
22 played an effect if what Dr. Kirkwood told us is correct?

23 PROFESSOR GROB: Well, this is an explanation
24 and a hypothesis which was provided by Dr. Kirkwood. I
25 would say I don't share this explanation because really I

1 don't think that either IL-2 or chemotherapy or interferon
2 can really change the overall survival. At least this has
3 not been established in the literature, neither in my
4 experience.

5 DR. SCHILSKY: Dr. Simon?

6 DR. SIMON: I had a few questions. One is you
7 indicated there were 35 patients who withdrew from
8 treatment. How were they handled in the analysis?

9 DR. HOOFTMAN: You're asking a question about
10 the 35 patients --

11 DR. SIMON: Yes.

12 DR. HOOFTMAN: -- the 14 percent who withdrew
13 from treatment?

14 DR. SIMON: Right.

15 DR. HOOFTMAN: As usual, they were all
16 included.

17 DR. SIMON: Their follow-up continued as for
18 the patients who did not withdraw from treatment?

19 DR. HOOFTMAN: That's correct.

20 DR. SIMON: I would like to get some
21 clarification about the database that was used for the
22 analysis, not for the interim analysis because my
23 experience is at a time of interim analysis, there are
24 delays in reporting and that's really not necessarily a
25 very accurate database, particularly in a multi-center

1 study with many centers involved and particularly when
2 you're using something like a triangular test in which the
3 protocol says you do analyses after every 20 recurrences.
4 I don't really think that's practical in a multi-center
5 study, and I have questions about the accuracy of the
6 database in a situation like that. So, I would like
7 clarification. So, for me, that's really not the
8 definitive analysis.

9 I would like clarification of what additional
10 follow-up was performed and what kind of auditing was done
11 and how long each patient was followed and what proportion
12 of the patients were lost to follow-up not for the interim
13 analysis but for the subsequent analysis.

14 DR. HOOFTMAN: I understand the question. Can
15 I give the work to a statistical colleague who was
16 intrinsically involved at the time?

17 DR. RAMISIO: My name is Dr. Maurizio Ramisio,
18 statistician, Hoffmann-La Roche, Basel.

19 The database that was used for the third
20 sequential analysis is unfortunately not available anymore.
21 We collected complete information on all the patients in
22 the beginning of 1996 and, as Dr. Hooftman said, getting a
23 new informed consent from all the patients. The follow-up
24 analysis that has been presented is based on those data.

25 The triangular test analysis that has been

1 presented is based on the data of the 1st of January 1994,
2 which are not available any longer.

3 We have simulated an analysis at the time of
4 the 1st of January 1994 by putting a cutoff, using the data
5 that we have to date, but putting a cutoff on the 1st of
6 January 1994. The result that we have got with this
7 analysis is still significant, is 0.035 on the log rank
8 test. But again, we are not able to reproduce the analysis
9 of that time.

10 DR. SIMON: So, the .035 represents an
11 estimated significance level at the time that that interim
12 analysis was performed?

13 DR. RAMISIO: This is what I'm saying now.
14 What has been presented by Dr. Hooftman is the result which
15 was obtained by Professor Chastung at that time doing the
16 third sequential analysis on the data which was available
17 at that time.

18 DR. SIMON: Suppose we forget about sequential
19 analysis. Can you just clarify what is the most complete
20 data available?

21 DR. RAMISIO: All right. The most complete
22 data available is the data that have been collected in the
23 beginning of 1996, and this is the data that have been
24 presented as follow-up analysis by Dr. Hooftman.

25 As I said before, if we do a cutoff on that set

1 of data, which has been quality controlled, and source
2 documents verified, and we do the analysis as it would have
3 been done on the 1st of January 1994. We get a log rank
4 test with 0.035 percent.

5 DR. SIMON: Suppose you don't do a cutoff and
6 you just do the analysis with all of the data.

7 DR. RAMISIO: If we do the analysis with all of
8 the data -- I don't remember what was the significance. If
9 we do the analysis on disease-free interval, including all
10 the patients, so intent-to-treat, including all the 499
11 patients, we have to exclude 2 who had no follow-up visit
12 at all. They went into the study. They were randomized
13 but had no visit at all. So, if we analyze that -- I'm
14 sorry. I must find the right page.

15 Here. The disease-free interval -- the
16 significance, stratifying by center, is 0.074. If we do
17 the analysis on the eligible patient population, so
18 excluding the 10 patients that we have discussed about
19 before, we get a p value, which is 0.035. This is
20 including all the data available up to the beginning of
21 1996.

22 If we do the analysis as it was prescribed by
23 the protocol, we said an analysis will be performed at the
24 end of the study, which could be interpreted as when all
25 the patients will have had 3 years follow-up. The p value

1 | becomes 0.005.

2 | Is this answering your question?

3 | DR. SIMON: What was the last point? If you do
4 | what?

5 | DR. RAMISIO: The protocol prescribed a primary
6 | analysis, which was the sequential, and said, unfortunately
7 | a little bit unclearly, a further analysis will be
8 | performed at the end of the study. So, it is a matter of
9 | interpretation what is the end of that study.

10 | In another place, the protocol says the
11 | patients will have to be followed for 3 years. So, an
12 | interpretation of the end of the study might be when all
13 | the patients will have been followed for 3 years. So, if
14 | we do an analysis cutting all the data following the 3
15 | years, so treating is censored all the patients who had a
16 | relapse after the 3 years, we obtain a log rank test with a
17 | p value of 0.005.

18 | If we do not do that, if we take all the data
19 | considering a median follow-up of 4.4 years, where some
20 | patients have been followed up for 3 years and some have
21 | been followed up for 6 years and more, then we get, on the
22 | eligible patients population, a p value of 0.035 and, on
23 | the ITT population, a p value of 0.074.

24 | DR. SIMON: One other question. You didn't
25 | present any data on sites of recurrence, which ones were

1 resectable, which weren't. Do you have that data?

2 DR. HOOFTMAN: Yes, we have that information.
3 We just have to find it.

4 As you can see here, the recurrences were
5 mainly regional or local as opposed to visceral.

6 DR. SCHILSKY: Dr. Blayney.

7 DR. BLAYNEY: Thank you. I have three
8 questions.

9 As has been alluded to earlier, in an analysis
10 where you're looking at disease-free interval, there's a
11 potential for bias introduced into the ascertainment of the
12 data points because patients may be lost to follow-up, the
13 ones that recur may die without knowledge of the
14 investigator. Without a prospective plan for follow-up,
15 this is of some concern in trying to interpret the data. I
16 guess I would have some more comfort if you could tell me
17 how many patients were lost to follow-up and how these were
18 handled in your analysis.

19 DR. HOOFTMAN: Please bear with us until we
20 find that information.

21 Can I defer this question to Dr. Sam Givens?

22 DR. WASSNER: We only lost something like 6
23 patients to follow-up in the long-term follow-up in the no-
24 treatment arm and 8 patients in the treatment arm over the
25 7 years of the trial.

1 DR. BLAYNEY: So, since those numbers are
2 equal, I'm understanding that there's probably a -- or
3 roughly equal, there's no bias, likely there would be no
4 follow-up bias in that.

5 DR. WASSNER: No. And less than 2 percent of
6 the patients have been lost to follow-up over this period.

7 DR. BLAYNEY: In your slide number 111, you
8 have a p value of .038. Now, maybe Dr. Simon's question
9 got to this issue, but is that p value adjusted for
10 multiple analyses?

11 DR. WASSNER: Yes. This value has been
12 adjusted only for that, only for the multiple analysis, not
13 for any prognostic factors.

14 DR. BLAYNEY: Thirdly, why did you choose or
15 why was it chosen to give patients 3 million units and not
16 adjust based on body surface area or some other measure of
17 size?

18 DR. HOOFTMAN: The decision by the clinicians
19 separately for the French study, as well as for the
20 Austrian -- they made that decision separately and not
21 knowing from each other what they exactly were going to do
22 -- was based on the fact that they were looking for the
23 dose that could be maintained for a long time and the lower
24 dose that was effective, which was 3 million units, as used
25 in other indications, for example, hairy cell leukemia, at

1 the time.

2 DR. SCHILSKY: Let me just make a comment to
3 the committee. I'm bound and determined to keep us on
4 schedule this afternoon because I know that some committee
5 members will have to be leaving. So, we have about 3
6 minutes left for questions. So, let me just ask you to
7 just keep your questions very focused.

8 Dr. Raghavan, do you have a question?

9 DR. RAGHAVAN: I just wanted clarification of
10 one quick thing. I think I understood somebody from the
11 sponsor to say the database is no longer available. What
12 does that mean and why?

13 DR. GIVENS: What that means is that they did
14 not save the database when they did the publication. They
15 kept adding to the database and making corrections. So,
16 the database as of today is the most up-to-date that we
17 have, but we don't have a copy of precisely what they used
18 when they did the sequential analysis, which is why we went
19 back and said, let's cut off all data that should have been
20 collected on visits up until the 1st of January and do the
21 analysis again.

22 DR. SCHILSKY: Dr. Nerenstone?

23 DR. NERENSTONE: Very briefly, first of all,
24 was there central pathologic review?

25 DR. HOOFTMAN: No, there was not.

1 DR. NERENSTONE: We've heard about how many
2 patients were withdrawn because of adverse experiences.
3 However, you have no information about what actual dose was
4 given, what kind of delays there were in the patients who
5 were on treatment for specific toxicity or even for the
6 asthenia, depression, and flu-like symptoms. Do you have
7 any other data available about that?

8 DR. HOOFTMAN: Yes, we have. We have
9 information with regard to dose reductions. About 83
10 patients, 33 percent, in the Roferon arm had their dose
11 reduced temporarily.

12 DR. SCHILSKY: Any other questions from the
13 committee?

14 (No response.)

15 DR. SCHILSKY: If there are none, then let's
16 break for about 14 minutes and reconvene promptly at 3:15.
17 Shorter if we can.

18 (Recess.)

19 DR. SCHILSKY: We'd like to continue with the
20 FDA presentation.

21 DR. CARDINALI: Good afternoon. My name is
22 Massimo Cardinali. I will introduce the FDA perspective on
23 this application.

24 First, I would like to acknowledge the review
25 team that worked on this application. Dr. Neeman did the

1 bulk of the statistical review, and Dr. Tiwari also
2 participated in the review. Dr. Gupta in the last week or
3 so did some additional analysis.

4 This slide is to remind the approved indication
5 for this product. The indication for the hairy cell
6 leukemia has the closest dosage to the one that the company
7 is seeking for this application.

8 This is the indication that the company is
9 seeking for this product as presented in the submission.

10 I'll briefly go over the events that took
11 place. You see in white the company and in yellow the
12 agency. The supplemental application was submitted in
13 1997. The company provided us with the translated protocol
14 and statistical plan and database for the Grob study, as
15 well as the available literature at the time on the subject
16 and an unpublished report. This was the study WHO 16, the
17 Cascinelli study.

18 We finished our review in March of '98, and Dr.
19 Neeman asked the company for some additional information on
20 the Grob study and that was received in May of that year.

21 The monitoring of the French centers was
22 completed in May of '98.

23 We issued a complete review letter in August of
24 that year. The database and data that the company provided
25 was perceived to be not sufficient for approval by the

1 agency, and we requested a database for the other study
2 with Roferon that was available, as well as some additional
3 clarification on the Grob study. The information was
4 provided in November of that year, and the paper for the
5 Pehamberger study was submitted to the application in March
6 of '99.

7 We received about a month ago the translated
8 study protocol for the Pehamberger study and early this
9 month the data set that Dr. Gupta analyzed.

10 I will go briefly to the structure of the two
11 studies. The Grob study was conducted between 1990 and
12 1994.

13 The inclusion criteria, essentially patients
14 with AJCC stage II and no previous therapy was in the
15 provision of the protocol. And the performance status was
16 set as ECOG less than or equal to 2.

17 The endpoint specified in the protocol,
18 disease-free interval, and as secondary endpoints, overall
19 survival and tolerability of the treatment.

20 The dose administered was 3 million units 3
21 times per week subcutaneous for a total duration of 18
22 months.

23 The study conducted in Austria was started
24 approximately at the same time and the same duration than
25 the French study. The inclusion criteria were almost

1 identical in terms of the staging of the disease. There
2 was no systemic therapy within 3 months of inclusion in the
3 study and the performance status was a little more
4 stringent.

5 The material that we received did not specify
6 the endpoint, and there was no statistical plan in the
7 protocol.

8 Again, the studies are very similar. The
9 difference that we can observe is the duration of the
10 treatment. The study had an induction phase of a 3-week
11 duration and then it was continued at 3 million units 3
12 times per week for a year.

13 I'll leave the floor to Dr. Lachenbruch that
14 will summarize the results and the statistical analysis.

15 DR. LACHENBRUCH: Thank you. I'm almost an
16 imposter up here in that the primary analysis was done by
17 Dr. Neeman at the FDA and then later Dr. Tiwari did this
18 work.

19 The study by Grob, M 23031, is the primary
20 trial that was submitted to the FDA. This trial was
21 planned to have sequential looks every 20 events. However,
22 the timing was not adhered to and three looks were done.

23 As you can see here in a triangular test, a
24 score Z is computed, and if the null hypothesis is true,
25 that will be around 0, and a variance V is also computed

1 | which is proportional to the number of events at the time
2 | of analysis. If the points exceed the upper boundary, the
3 | null hypothesis is rejected, as you see. On January 1st,
4 | '94 when the analysis was done, it did exceed the null
5 | hypothesis.

6 | During the FDA review, we requested that the
7 | sponsor submit more mature data from the additional follow-
8 | up that they have, and our analyses are all based on an
9 | intent-to-treat at this time of final analysis.

10 | This is a graph you've seen before. The
11 | medians are indicated. Because the number of relapses at
12 | and before this time of the medians, the estimate of the
13 | medians may be somewhat variable. This again is based on
14 | the ITT population and not the per-protocol population.
15 | This results in an additional 9 patients being added to the
16 | overall population, and the significance level that we see
17 | here is .095 as opposed to the .038 from the sponsor's
18 | analysis. This is no doubt due to both the additional
19 | data, more mature data, and the additional patients.

20 | The overall survival is shown here, again with
21 | the ITT population. We came up with a .09 p value.

22 | We also decided to examine some additional
23 | analyses which are exploratory, and these are, indeed, post
24 | hoc but I think they are of some importance. This slide
25 | shows the effect on relapse-free survival of the covariate

1 alone, and that's important to realize. Thus, the Breslow
2 thickness has a p value of less than .001. That is for the
3 effect of Breslow thickness on survival. It is not a p
4 value for Roferon given Breslow thickness.

5 Among these data, the p value for Roferon is
6 larger, i.e., less significant, than for any of the others.
7 Also, I should point out that Dr. Neeman used the Breslow
8 thickness as a continuous rather than as a categorical
9 variable.

10 We also attempted to find a best model for
11 using the covariates, and in this case we found that
12 Breslow thickness, age, and sex gave the best model.
13 Adding Roferon treatment to those three led to a p value
14 for Roferon of .25. The sponsor, Roche, did do a similar
15 analysis. They dichotomized age as greater than 50 or less
16 than 50. The differences may be due to more mature data,
17 the use of age, or the additional patients.

18 The results are marginal significance. The p
19 value at the time of the termination of the study is .038,
20 but after the data had matured, it was .095.

21 We received the Pehamberger data last week, and
22 we have been unable to do a detailed and rigorous analysis
23 of the results. We received a translation of the protocol
24 about a week earlier.

25 We attempted to reproduce the analyses that

1 appeared in the article and will present some comments.
2 The inclusion criteria, of course, are essentially the same
3 as for the Grob study. The analytic plan was not presented
4 in the protocol and endpoints were not specified. We used
5 relapse-free survival and overall survival, and we've also
6 done some adjustments for Breslow depth and did a
7 corresponding analysis including age and gender as we did
8 with the Grob study.

9 Here we see the relapse-free survival, and we
10 found a p value of .04 and median for controls is 4. The
11 Roferon group did not reach a median.

12 In doing the same proportional hazards model,
13 we find quite similar results. Breslow thickness is highly
14 significant; age, significant; sex, somewhat less; and
15 Roferon as, of course, .04.

16 At the same time we did the adjustment for
17 Breslow alone, which is what was reported in the
18 Pehamberger article, and found a p value of .1, and if we
19 adjust for Breslow thickness, age, and sex, we had a p
20 value of .22, quite similar and comparable to the p of .25
21 that was seen in the Grob study.

22 Again, our conclusions seem to show that there
23 was a moderate effect of Roferon by itself, which is the
24 primary analyses that are presented by the company.
25 However, adjusting for Breslow thickness and other

1 | variables does seem to reduce the effect.

2 | Based on this, we felt that it was appropriate
3 | to begin planning an overview of the published literature.
4 | So, we are doing this to combine the evidence. What we
5 | want to do is substantiate the evidence of efficacy from
6 | known studies of adjuvant interferon in melanoma, and for
7 | this purpose, we will use studies of both Roferon and
8 | Intron. These are exploratory and we want to emphasize
9 | that the data support from Roche will be the only material
10 | that is used in any decisions regarding this product. We
11 | will be using relapse-free survival and overall survival,
12 | as they are the generally accepted outcomes. And we are in
13 | the process of obtaining data from investigators.

14 | We will be looking at Roferon and Intron
15 | trials. We want them to be randomized, concurrent
16 | controlled trials, and so far all have an observational
17 | control and are for adjuvant therapy.

18 | We have searched a number of databases seen
19 | here. The trials that we have identified and the studies
20 | come from North America, Europe, Australia, and New
21 | Zealand. We will be looking to get estimates of the odds
22 | ratio by means of ratio of medians, and that's very nice if
23 | you happen to have exponential survival. That's for the
24 | statisticians. And the Peto method is basically a log rank
25 | type method.

1 We will also be looking for estimates of
2 survival, either relapse-free or total survival at 3 years.
3 We'll be looking at Kaplan-Meier estimates, 95 percent
4 confidence intervals, and so forth.

5 So far the studies that we have found are those
6 from Dr. Creagan, Dr. Cascinelli, Dr. Grob, Dr.
7 Pehamberger, which all were using Roferon. We've seen five
8 studies from Kokoschka, Kirkwood, Cornbleet, Rusciani, and
9 the Kirkwood ECOG 1690.

10 This slide provides estimates of the percent
11 improvement and confidence intervals for relapse-free
12 survival that we have seen thus far. A square is placed at
13 the estimate for the difference in proportions. The
14 whiskers are the 95 percent confidence intervals. A
15 positive value is favorable for interferon. So, if the
16 whiskers cross the line, it is not possible to rule out a
17 difference of 0 between observation and interferon.

18 The size of the box, that is the area, is
19 proportional to the sample size. These generally indicate
20 a consistent improvement of about 8 to 9 percent over
21 observation. We don't have reliable 5-year data at the
22 present time to conduct a similar display.

23 In overall survival, we see the same picture.
24 As you can see, there's a bit less of an impressive
25 difference in these. We did not have the data from Dr.

1 Pehamberger for survival. The difference is around overall
2 about 4 to 5 percent.

3 Our next steps will be to get individual data
4 from studies and perform the analyses that we have
5 indicated above. The information contained in the
6 literature does not permit sufficiently detailed analyses.

7 To summarize, for relapse-free survival, all
8 studies do point in the same direction. These are
9 marginally significant or barely not significant, and
10 there's a moderate early effect. But we don't have a lot
11 of data for longer term effects.

12 For overall survival, there is a consistent
13 trend toward improvement but evidence is not that strong,
14 and I have in my notes, parentheses, "yet" with a question
15 mark. We did not show it, but there do seem to be fairly
16 similar results with high and low dose and with node-
17 positive and node-negative disease from the material that
18 we've seen.

19 Thank you.

20 DR. SCHILSKY: Thank you very much.

21 Questions for the FDA? Dr. Raghavan?

22 DR. RAGHAVAN: I'm totally mystified as to why
23 you went through that statistical exercise because the best
24 data points come from a product that isn't even up for
25 submission. So, I just wondered why you spent all your

1 | time doing this and what the point was.

2 | DR. LACHENBRUCH: The purpose here was to
3 | really look for evidence combining all of the Roferon data.
4 | Over here, we see that there are four studies, and so what
5 | we would like to do is be able to draw information from all
6 | of these. So, what we see is overall there does seem to be
7 | a significant improvement in 3-year survival.

8 | DR. SCHILSKY: Other questions? Dr. Simon?

9 | DR. SIMON: I guess I wouldn't put much
10 | credence in a meta-analysis based on literature data.
11 | There may be exclusions. There are all kinds of biases in
12 | published reports. The fact that they're published may be
13 | publication bias. If you're planning on doing an
14 | individual case meta-analysis, I would say go ahead and do
15 | it, but I don't find it useful to present a meta-analysis
16 | based on publications.

17 | DR. LACHENBRUCH: These are very preliminary
18 | results, and we are trying to get the data at the present
19 | time. So, I would agree with you.

20 | DR. KEEGAN: I think to some extent the reason
21 | why these data were presented was that up until very
22 | recently, the only information we had was from a single
23 | study. So, this was our attempt to see what other
24 | information was available in support of this application.
25 | We're not saying it's optimal information, but it was all

1 that we had available.

2 DR. CARDINALI: As a note, the Pehamberger and
3 Grob study data is from the publication not from the data
4 set we have analyzed.

5 DR. SCHILSKY: Dr. Simon.

6 DR. SIMON: Do you have any insight for the
7 French study as to why the significance level, say, for
8 relapse-free survival, after adjustment for thickness, age,
9 and sex, changed so much? Were there any imbalances?

10 DR. LACHENBRUCH: No. For a covariate
11 analysis, as you know, the purpose is not necessarily to
12 adjust for imbalance, although that can be one use of it,
13 but these happen to be important prognostic factors for
14 survival. So, what we're saying is we'd like to look at
15 these after we have adjusted for these.

16 DR. SCHILSKY: Dr. Lippman.

17 DR. LIPPMAN: Just a quick clarification. In
18 your last conclusion slide, you said that there were
19 similar results with high and low dose. Is that what we
20 just saw from Dr. Kirkwood with Intron or is that with
21 Roferon?

22 DR. LACHENBRUCH: I believe that was the for
23 the Roferon, the study of Dr. Creagan and the Grob and --

24 DR. SCHILSKY: Other questions from the
25 committee members?

1 (No response.)

2 DR. SCHILSKY: Okay, thank you.

3 Let me point out to the committee members that
4 there's a slightly different set of questions than the ones
5 that were in the blue folder, and those should have been
6 put at your place right after lunch. It looks like this.
7 It's a two-page thing. It has only one of these meta-
8 analysis charts. I think the content of the questions is
9 largely the same, but these are the questions that we
10 should be focusing on at this point.

11 Before we get into the questions, actually I'd
12 like clarification of one point from the FDA because most
13 of these questions are posed in such a way that they ask us
14 to consider the results of the sponsor's data in
15 conjunction with the overview analysis that was just
16 presented. Now, I was quite sure I heard the FDA presenter
17 say that the overview analysis would not be taken into
18 consideration by FDA in assessment of the sponsor's
19 application. So, could we get some clarification on that?

20 DR. LACHENBRUCH: Yes. What I said was no
21 Intron data would be taken into account.

22 DR. SCHILSKY: I see. It's a little bit
23 difficult for us to sort out from those meta-analyses which
24 ones had Intron data and which ones had Roferon data.

25 DR. SIEGEL: Let me clarify something. First

1 | of all, the Roferon data were the top part of all those
2 | slides and are on the second page of the questions.

3 | The FDA has a policy regarding use of
4 | literature in support of applications for new indications
5 | for already approved drugs. The gist of the policy says
6 | that literature data, especially if consistent and
7 | compelling from multiple sites, can be important, but the
8 | value of the data is largely dependent on the ability to
9 | substantiate it through finding protocols, data sets,
10 | ensuring that there were intent-to-treat analyses, and the
11 | normal things. So, these are things I think that, as a
12 | matter of policy and procedure, should not be ignored, but
13 | I think that the weaknesses or concerns that have been
14 | highlighted are important ones to take into account.

15 | DR. SCHILSKY: Okay, thank you.

16 | Maybe we'll just get on with the questions
17 | then. Yes, Scott.

18 | DR. LIPPMAN: I know that we're not considering
19 | Intron here, but I think the data are relevant in the sense
20 | that -- two issues. One is the biological plausibility
21 | mechanism and the other is consistency within the committee
22 | in terms of approval.

23 | Again, we talk about the fact that there's very
24 | little data. So, we have one study of 500 patients which,
25 | at least in the FDA presentation, we've talked about those

1 | mysterious 9 cases and how that would affect. But at least
2 | in the FDA presentation, it was significant. Every one of
3 | the boxes is -- it's modest, but it's positive both in
4 | terms of disease-free and overall survival, and the
5 | whiskers come very close, just past the survival curve of
6 | 0, as opposed to another situation where we're using
7 | interferon where it's approved and where you don't see that
8 | pattern even with a very high dose in terms of survival.
9 | And we've heard some explanations of that. It's really a
10 | question of whether we should take that issue, the
11 | consistency, the biology, the mechanism, into account in
12 | some of these discussions.

13 | DR. SCHILSKY: I don't think we should ignore
14 | the universe of information that we're aware of and we have
15 | available to us.

16 | I just want to get clarification on this again.
17 | First of all, the meta-analyses with respect to the Roferon
18 | data, which is what's on our question sheet -- so, there
19 | are four studies listed for disease-freed survival and
20 | three listed for overall survival. Of those, only the Grob
21 | study would appear to show a significant benefit with
22 | respect to disease-free survival as it's listed here.
23 | However, as the more detailed analysis of the study was
24 | presented to us, there are questions as to, in fact,
25 | whether even that study shows a significant difference in

1 disease-free interval. So, although the trend appears to
2 be in favor of interferon in each of these examples,
3 there's very little in the way of a statistically
4 significant benefit for interferon.

5 Further, it's fair to say that, I guess, in a
6 sense these are at best incomplete meta-analyses for the
7 reasons Dr. Simon mentioned, that this information is just
8 based upon data you could glean from published reports in
9 the literature, not from the actual patient data that's
10 contained within those reports. Correct? Okay.

11 Scott?

12 DR. LIPPMAN: Just to clarify, because with all
13 the discussion, I guess I was sort of surprised when I look
14 at this. I'm not talking about the meta-analysis, just the
15 big box of 500 patients under Grob. It is significant,
16 doesn't cross the line. I haven't read the recent set of
17 questions, but one of them was should we recommend approval
18 based on one large randomized trial. So, I'd like to
19 clarify maybe from the FDA if they're going to stick with
20 this box. In that case, that is statistically significant
21 and survival is close and the other studies corroborate
22 that. So, I'd just like to clarify.

23 DR. SIEGEL: Well, I guess a lot of people have
24 addressed different parts of this question. I'll take my
25 turn.

1 That box was an endpoint that was chosen in
2 part because it was, I think, the easiest endpoint to get
3 on all of the trials, and it's endpoint data truncated at 3
4 years. That's the endpoint that the Grob data looked the
5 best at because, in fact, the curves have maximal
6 separation at about 3 years and start coming together after
7 3 years. As noted, that studied had 3 years of planned and
8 prescheduled follow-up, so it's not an irrelevant time
9 period for that study. But at best, let's say that the
10 primary time for follow-up is ambiguous in the protocol and
11 difficult to determine. As we determine it, the intent-to-
12 treat analysis of the most complete available data set was
13 at the .095 level and with covariate correction at the .25
14 level.

15 We'll stand behind that analysis. It's one of
16 several analyses. We won't stand behind it as like the one
17 that tells the story. I don't think, given the ambiguities
18 of the protocol and the flaws and strengths of different
19 analyses, that there's probably not one p value that you
20 can hang your hat on and say this tells you the statistical
21 significance of the trial.

22 DR. SCHILSKY: Are we ready to go to the
23 questions? Let me just read the first question. There's a
24 two-paragraph summary. Then the question is, does the
25 committee find that the results of a single multi-center,

1 | randomized, controlled trial, in conjunction with the
2 | overview analysis of the three randomized, controlled
3 | trials of Roferon-A, provide substantial evidence that
4 | Roferon-A prolongs the disease-free interval in patients
5 | with surgically resected melanoma?

6 | Is there discussion on that before we vote?

7 | Dr. Lippman.

8 | DR. LIPPMAN: I will just say that the real
9 | fundamental issue that I'm having a problem with is the
10 | floating p values. Given that we've heard a lot of
11 | discussion on this and still know real consensus, I don't
12 | think, in terms of what is either reasonable or meant or
13 | intended, that's going to fundamentally affect how I vote
14 | anyway on this.

15 | DR. SCHILSKY: Well, I think we've seen the
16 | data as presented by the sponsor. We've seen the data as
17 | presented by the FDA with the adjustments to the p value,
18 | if you will, based upon the other covariate prognostic
19 | factors. We've seen, for what it's worth, the preliminary
20 | meta-analysis. So, is there anything else you would like
21 | to know before you vote on this?

22 | DR. LIPPMAN: I think fundamentally if we knew
23 | exactly in the design what the primary endpoint was -- was
24 | it a 3-year? I think that's where the debate is.

25 | DR. SCHILSKY: It appears that we don't know

1 | that because it wasn't well specified.

2 | DR. KEEGAN: That's correct. The protocol
3 | really is open to quite a bit of interpretation as to when
4 | that final analysis was to have occurred and exactly what
5 | it was to consist of.

6 | DR. SIMON: I will say, however, that my
7 | experience is if you have an endpoint, that your most
8 | accurate analysis is the one based on the longest follow-up
9 | and that's what you should hang your hat on and not one
10 | that was simulated based on what might have happened some
11 | years ago. So, anyway, I guess that's one issue.

12 | The other issue is for myself I guess I just
13 | have some basic uncertainty about the quality of the data
14 | from that trial, the potential biases in follow-up. It
15 | looked like there was too much of an emphasis that the main
16 | analysis would have been the one that was essentially an
17 | interim analysis that stopped the recruitment. Then there
18 | were sort of ad hoc attempts to increase follow-up. I just
19 | am left with some uncertainty as to how accurate that
20 | additional follow-up was. So, I myself, in addition to the
21 | variable p values, just have some uncertainty in the
22 | credibility of that data.

23 | DR. SCHILSKY: Dr. Keegan.

24 | DR. KEEGAN: I would say that the protocol did
25 | not specify what the continued follow-up should be after 36

1 months, and when we requested the additional data, it was
2 necessary for the company to go back to the investigators,
3 who then reconsented patients to get the information. From
4 the monitoring inspections of some of the sites, it's clear
5 that there wasn't a rigidly adhered to schedule for follow-
6 up.

7 We did also ask the company to analyze the data
8 to determine whether or not there was a systematic bias in
9 terms of the follow-up, and it didn't appear that the
10 follow-up was systematically biased towards one or the
11 other arm. It was equally -- I won't characterize it as
12 haphazard, but definitely not done according to a rigid
13 schedule. But that seemed to be present in both arms.

14 One other point I'd like to make in terms of
15 the policy is that for a single study in support of
16 effectiveness, one of the criteria that FDA uses is that
17 the trial have a statistically significant result that's
18 fairly robust such that we would have confidence that the
19 result would be reproducible. At best, the p value here is
20 .04, and our concern at the time of even the review of the
21 data with the most up-to-date follow-up that we could get
22 through 1997 suggested to us that that result, although
23 statistically significant, would not meet that condition of
24 being so robust that we were convinced that it was a
25 reproducible result, which is why we encouraged the company

1 to go back and obtain additional study data.

2 DR. SCHILSKY: Dr. Johnson?

3 DR. JOHNSON: Yes. I didn't realize this was
4 going to take a lot of discussion, but since Scott seems
5 conflicted, let me go through a number of reasons why I
6 think this is a poor study.

7 First of all, I'm not sure I accept the
8 endpoint as one that's therapeutically efficacious. DFI,
9 in the absence of a survival benefit, is of uncertain
10 benefit in my view. We can debate that but there are
11 plenty of diseases where DFI can be prolonged and survival
12 is not. And we don't do the therapy that prolongs the DFI.
13 Small cell lung cancer immediately comes to mind. There
14 are 10 randomized trials out there showing DFI is
15 prolonged, survival is not. No one uses maintenance
16 chemotherapy in that disease.

17 If they had shown me some quality of life
18 benefit to that DFI, that symptoms had improved or some
19 other meaningful patient benefit, then perhaps I could have
20 accepted that as an endpoint of value, but I don't. And I
21 didn't see that data.

22 Thirdly, again, I find it shocking -- and I
23 think that's the word -- that a study of this size would be
24 undertaken without appropriate stratification for known
25 prognostic endpoints. That being said, even more

1 | importantly, there was no quality control of pathology. We
2 | have no idea whether these patients were equally balanced
3 | other than what they tell us. There was no central review
4 | of the patient pathology. They could have all been one
5 | stage in the Roferon arm and quite another in the other,
6 | just on the basis of that inequity. All we have is a
7 | report. They've told us there was no central pathology
8 | review.

9 | Candidly, I just think that the overall data
10 | are highly questionable. I agree with Richard. I think
11 | these are not the quality of data that we see come to this
12 | agency that generates approval by this body. That's my
13 | perspective on this, and personally I don't see how we can
14 | vote anything other than no on this question.

15 | DR. SCHILSKY: Dr. Raghavan?

16 | DR. RAGHAVAN: Yes. I think I always feel
17 | sorry for the FDA because they're victims and they get
18 | beaten up by everyone, but as a taxpayer I really have to
19 | say that I don't think you've done as well as you usually
20 | do this time. You've left it to the committee to identify
21 | a whole series of very bad statistical concepts and poor
22 | quality data. I shouldn't have to remind you: garbage in,
23 | garbage out no matter what the p value. I just feel very
24 | disappointed that we've had to go through this exercise.

25 | Dr. Lippman has tried very hard to be fair, and

1 I recognize and respect that. For those of us who are
2 crusty veterans who have seen outstandingly good data over
3 the years, this is not an example of that. And bending
4 over backwards to bring in Intron data that were approved
5 based on good quality data and then tainting that
6 information based on very poor quality information with bad
7 follow-up sets up a precedent that that I think is kind of
8 disappointing. And I would hate people to leave here
9 starting to question decisions made in the past based on
10 good data when we've now added a bunch of information
11 that's out-of-date, hard to quantify, irreproducible, et
12 cetera.

13 And I just felt I wanted to make that comment.
14 I apologize for beating you up, but you deserve it.

15 (Laughter.)

16 DR. SIEGEL: Allow me to respond in part,
17 although I don't want to take up too much time with this.

18 First of all, I think it's a
19 mischaracterization to suggest that it took the committee
20 to identify the flaws in this data. I don't think there
21 was a flaw discussed here that was not identified by the
22 FDA. The FDA did an intent-to-treat analysis from the
23 beginning. We carefully inquired and investigated about
24 the relevance of the follow-up data, the quality of the
25 follow-up data, and the choice of the endpoints, and made a

1 presentation of the data, I think, that accurately reflects
2 our perception.

3 As to the question of why these data were
4 brought before the committee, perhaps this requires a bit
5 of understanding of time lines. At the time we need to
6 make a decision about scheduling a committee, it's usually
7 a couple months before the committee. As we have made
8 clear in the presentation, we had felt that based on the
9 Grob study alone, there was no reason to discuss or
10 consider approval of this application.

11 What we had available to us at the period two
12 months before this committee was a published report from
13 the Pehamberger study that showed a p value of .02 and new
14 information from the company that they were, in fact, going
15 to be able to get the data set and the protocol. Those, as
16 you've heard, I'm sure for a good reason, took longer than
17 anticipated to get. So, they arrived within the last week
18 or two. You've seen the preliminary analyses of those.
19 The study did not look like what we expected it to look
20 like, but I think with that perspective, perhaps you can
21 better appreciate where we've come from.

22 DR. SCHILSKY: All right. Thank you.

23 In the interest of time, I'm going to call for
24 the vote. I think we're probably ready. Let me just
25 restate briefly the question. Does the committee find that

1 | the results of a single multi-center, randomized,
2 | controlled trial provides substantial evidence that
3 | Roferon-A prolongs the disease-free interval in patients
4 | with surgically resected melanoma?

5 | All those who would vote yes, please raise your
6 | hand.

7 | (No response.)

8 | DR. SCHILSKY: That's 0 yes.

9 | All those who would vote no?

10 | (A show of hands.)

11 | DR. SCHILSKY: 7 no.

12 | Abstentions?

13 | (A show of hands.)

14 | DR. SCHILSKY: 1 abstention. Sorry. 2
15 | abstentions.

16 | DR. SIEGEL: I think we're done.

17 | DR. SCHILSKY: That's what I was about to ask
18 | because the second question says, assuming that the answer
19 | to question 1 is yes, well, we know now what the answer to
20 | question 1 is. So, I think that completes the committee's
21 | deliberations. Thank you all very much.

22 | (Whereupon, at 4:02 p.m., the committee was
23 | adjourned.)

24 |

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