vote to approve this drug first-line, not a question of whether it's an active drug or not, or whether I think it's an active drug, but why would I do so, because it seems like I could add neurotoxicity to 5-FU.

MR. MOYER: So, your question is why first-line.

DR. D. JOHNSON: Right.

MR. MOYER: Dr. Rothenberg or Dr. Haller, would you like, or maybe both want to give your perspectives on that?

DR. ROTHENBERG: I think that is a question that we all have to grapple with, and I think the way I would phrase it is, is the adjusted analysis appropriate and more reflective of the true clinical situation.

I think the answer to that question is yes. I think that we know that in some cases, in this study and other studies, it wasn't so much the intervention that was being studied, but it was some other event that occurred either baseline or intervention that was not the focus of the study that had the major impact on those events.

I think that not taking those other events into account actually undermines the potential for the study to show any difference. So, that is why I think that it is important to take that into account.

I think it is also important to recognize the fact that when these trials were first designed, the appreciation

of the impact of second and subsequent therapy for these patients was not appreciated because it wasn't there, it wasn't available.

It became available for these patients, and as you can see, the vast majority of patients did pursue second- and third-line treatments, treatments that weren't available just a few years ago.

So, I think that the approach to these patients and the approach to the analysis of these kinds of data could choose just to take the first-line intervention into account and assume that that is going to have an effect throughout the entire course of a person's life or to be able to analyze the impact of first-line treatment in endpoints that are most likely to capture the impact of that first-line treatment.

I think these data are convincing to me because of their consistency, as well, in terms of response rate, progression-free, and overall survival, and I am encouraged by the length of the progression-free and overall survival that I have seen.

These were not single center trials done by people who are expert in giving this drug. These were multi-center trials done by people, many of whom were in community practice, who were able to attain progression-free survival of eight months.

Looking at that in context, the majority of advanced colorectal cancer trials that were done front-line have progression-free survivals that are very tightly restricted to a four, five, maybe six-month range. Here, we are seeing eight months.

Overall survival in multi-center cooperative group trials of 5-FU and various modulations of that have median survivals in the 11, 12, 13, even 14-month range. We are seeing median survival in excess of 15 and 17 months in these two trials.

So, I think that with the pivotal Phase III trial, as well as the seven supportive trials, I think that we have a body of evidence here that strongly suggests that oxaliplatin is a useful drug, and what we focused on is its impact in front-line treatment, also recognizing the fact that it does have some impact subsequently that may have actually obscured the front-line impact, but that is what we are focusing on right now.

MR. MOYER: Dr. Goldberg has actually struggled with this, and Dr. Haller can give his perspective, as well, because Dr. Goldberg struggled with this in the 6C trial and how to design that. So, we will let Dr. Haller make his comment and then maybe have Dr. Goldberg.

DR. HALLER: Just briefly, Dr. Johnson. In terms of the toxicity, what I hope I had left you with was a sense

that although there was an increased toxicity profile numerically, from a clinically relevant standpoint, from those of us who have given the combination frequently, it is a relatively easy combination to give, and as the patient representative said, the only thing that people do see in terms of neurotoxicity is that it is more entertaining than serious, that is, patients struggle to find words to describe the unique events that occur rather than complain of them.

In the time-to-treatment failure slide, the overwhelmingly larger reason for going off study was progression of cancer rather than intolerance of therapy. So, I think if one talks to clinicians who actually gives the combination, this is one of the easier combinations that I give in my own practice.

I think I would like to balance that out. The neutropenia numbers are impressive, but the febrile neutropenias are reportable, and the neuropathies are predictable and easily manageable with some foresight in management.

MR. MOYER: Dr. Goldberg, could you address what you have toyed with and struggled with on the 6C trial?

DR. GOLDBERG: When we designed the 6C trial, we went to the FDA to talk about endpoints, and I have to admit it was probably the most unpleasant two hours of my life,

because it was a difficult conversation.

You, like we, have to wrestle with the endpoints in clinical trials as you help to make decisions that will allow patients access to active drugs and protect patients from drugs that are potentially toxic and not effective and expensive.

We were able to sell the FDA on the idea of progression-free survival as the endpoint for the 6C trial, and the reasons that we were able to sell that were, one, the ODAC had recently recommended approval of CPT-11 in second-line therapy because it provided a survival advantage to patients over best supportive care or over second-line therapy with another 5-FU-containing regimen.

So, there was clear evidence that a second intervention in colon cancer could influence survival. In addition, there is an emerging literature about resection, salvage surgery as a means of curing some patients with colorectal cancer after they have manifest metastases.

That has heretofore been an unapproachable goal, but now is an approachable goal, and as you have seen demonstrated to you this morning, in aggressive centers, such as the Hospital of Paul Brousse, and also in Dr. de Gramont's experience, the ability to resect patients after treatment with oxaliplatin seems to be higher than it is with conventional therapies.

It is exceptional to see patients go to resection after 5-FU/leucovorin. It is not uncommon to see patients go to resection after treatment with oxaliplatin.

DR. SCHILSKY: We are going to take four more questions from the committee members, and that will be from Drs. Pelusi, Santana, Albain, and Margolin.

Jody?

DR. PELUSI: I would like to ask a question in regards to the toxicities. In terms of the study protocol, were there any protocols that dealt specifically with the management of premedications for each one, because as you said, it should take some good foresight in the beginning and I think direction in terms of making these treatments tolerable, in terms of symptom management is good.

My real question is if there were protocols for each of the toxicities or side effects for those people who experience Grade 3 and Grade 4 toxicities, what was the adherence to those protocols?

DR. HALLER: There were very clear guidelines for dose reductions in each of the protocols that you saw, and as I mentioned, one of the most important factors was that a trial-specific scale had to be devised. The NCI common toxicity scale now includes a Grade 4 neurotoxicity, which is the same as the Grade 3 trial-specific scale used in these studies.

They were adhered to quite closely, which is why most patients, in fact, tolerated their therapy quite well. If we look at the slide that deals with withdrawals, for example, Slides 15 and 16, it shows that in the pivotal trial 2962, S15 and S16, and 11 and 12, please.

[Slide.]

What this shows is the median exposure of patients having dose reduction or discontinuation of oxaliplatin for neurotoxicity, and essentially, as you remember, the median number of cycles for all patients was 11 for the control arm, 12 for the oxaliplatin/fluorouracil control arm. This is for neurotoxicity.

The total number of patients who got full-dose oxaliplatin was pretty close to the median, so this was a toxicity that occurred late, but as you can see, people got treated out to 26 total cycles.

So, with compliance with the criteria established in the study, people were able to continue treatment for quite a long period of time.

If I can see the next slide.

[Slide.]

This looks at the other major toxicity, hematologic toxicity. This occurs rather late, but again, one is able typically to continue a fairly long number of treatment cycles, and with any oxaliplatin, the number was

the same as for any patients in the total group of patients in the pivotal trial.

The other is that this has been something in evolution, and so there are now two large-scale trials, adjuvant trials with oxaliplatin worldwide. One is the NSABP CO7 trial, the other is the MOSAIC trial that has already accrued over 1,000 patients, and these both have trial-specific scales that take into account the dose modification criteria learned in the pivotal trial and learned in the initial monotherapy and combination studies.

DR. PELUSI: I guess I wasn't really looking at the dose reduction part of it. What I was looking at is in terms of when patients go on your studies, are there premedication regimes that are adhered to before they actually get there in terms of when I look on your page 81 of your handout, and you say basically 14 percent of patients went off therapy because of adverse events and 11 percent refused to go on to treatment, I always wonder what was the quality of their life or their experience with side effects.

So, my question again, based on what you had said earlier, is with some foresight, these are manageable, so I would hope that if there is this foresight out there, the question is those people that experience Grade 3 and 4, did they not have access to premedications or what guidance can

be given if you think that this is so helpful.

DR. HALLER: Let me show you a few slides. If I can have S-24, which just shows some of the supportive medications given during treatment.

[Slide.]

As you can see, because of increased diarrhea, there was somewhat more loperamide and octreotide used in this arm. In one center, they chose to use some neupogen although this is typically not required and in my experience I have never used the drug either prophylactically or therapeutically. Transfusions for anemia were relatively uncommon in either arm because anemia was not a significant toxicity.

So, the most significant toxicity was that myelosuppression is easily managed with dose reductions or dose delays. If you look at the neurotoxicity, this is something that in speaking with a patient each time they come and making the appropriate dose reduction, you can largely avoid.

I think if you look at one issue, which I think you are asking, which is the quality of life issue, in this study, in fact, EORTC quality of QLC, quality of life data were obtained. The problem is that compliance with the quality of life data was not extraordinarily good.

If I can see Slide B-101.

[Slide.]

So, there was an attempt to look at this. You can see about 75 percent of patients in both arms filled out their forms completely at onset.

Remember, most people made it out to here, the median patients made it out to here, so then only 50 percent of all the patients were filling the scales out at the eighth or ninth cycle, and if you take only those patients that started, it was less than 50 percent. So, we did not include it in the primary presentation because we did not think the data were reliable.

We did do another analysis just to add something to this, to give a flavor of what it is like to use this in the clinic. I can show you actually the next slide, which is B-109.

[Slide.]

Just to show you these are the data that were available, and you can see the number of patients out here is quite small. Here is the baseline. So, although the number here at the baseline starts to approach zero, the fact is that 90 percent of the patients in the study, as in most colorectal studies, start off with a normal performance status.

This is not pancreatic cancer where you expect increases. These people already feel well, and the goal is

to keep them feeling well, and on the whole that occurred in both treatment arms to the point at which the data becomes somewhat unreliable.

If I can see the last slide S-30.

[Slide.]

One thing we did look at is I do think that performance status is still a reasonable measure of a global performance status of the patient or global status of the patients, so we look at time to first decline.

Most patients were zero or 1, so this meant they went to 1 or 2, and if you look at the difference across the board, as I showed you for neurotoxicity, there was no difference whether you had it or didn't as to what your performance status is when you went off.

So, that even with the optimal therapy with the proper dose modifications, you don't see a big difference in the quality of life of patients as measured by these surrogates.

DR. SCHILSKY: Thank you.

In the interest of time, I just want to ask the committee members to focus your questions on new issues or new information that hasn't been previously discussed.

Dr. Santana.

DR. SANTANA: It's a follow-up of toxicity issues, and it has to do--can you clearly identify for us, because

there is a learning curve with all new drugs, the issue of neurotoxicity, besides preventing it or ameliorating by dose reduction, did patients require any other additional medical intervention to treat these neuropathies?

DR. HALLER: The answer is really, they do not. I think simply talking to your patient works. I have now sat down with--I have treated all of the patients at our institution personally, so I have sat through 700 separate discussions on what your neurotoxicity was like this week, and as I said, mostly, they are entertaining.

I have had no patients stop because of cumulative neurotoxicity, the dose reductions are effective, and most of the time they are as the patient described, something that is easily managed, dose reductions are typically not required for the very early transient toxicities.

When they begin to occur, they occur in the problem patients who are alive for long periods of time, who are receiving multiple cycles of drug, and then a discussion has to take place about the proper dose reduction or delays, and, in fact, there is a trial now ongoing in Europe, the OPTIMOX trial, to look at more intense oxaliplatin therapy upfront with a period of rest, if you will, built in to see whether or not this dose, toxicity can, in fact, be dealt with.

But in standard practice in the compassionate use

study in the United States and in the practice of our own patients, it really is not a very big problem.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: I am still having trouble understanding how the randomization occurred. How is the informed consent obtained? Please explain in a little more lay terms what this minimization technique involved.

MR. MOYER: As far as the informed consent, these studies were conducted not in the United States, but do meet the requirements of the Code of Federal Regulations as set forth in 314 and under informed consent under 52.

DR. ALBAIN: I don't understand those numbers. Could you explain how the informed consent was obtained?

MR. MOYER: Informed consent was obtained?

DR. ALBAIN: Yes.

MR. MOYER: Prior to randomization, informed consent was obtained for each patient. Now, as far as minimization technique, I will ask Steven Piantadosi, who can address the specifics regarding that technique, because I am not aware of that.

DR. PIANTADOSI: My name is Steve Piantadosi. I am a clinical trialist from Johns Hopkins Oncology Center. I am a consultant to the company on statistical matters.

I was not involved in the randomization of this study, so just to get that upfront. I came onboard later.

Minimization is a technique that is used actually quite extensively in slightly different forms for the assignment of patients to treatment arms in clinical trials, and basically attempts to guarantee that the treatment arms are comparable with respect to important prognostic factors.

In that sense, it is very similar to blocked and stratified randomization, but the algorithm that is used is a bit more complex. Typically, it would involve remembering all of the previous assignments onto the treatment arm in calculating some sort of overall score or prognostic effect, and then making the next assignment in a way that minimizes the difference in that prognostic expectation between the treatment groups.

I don't know which particular minimization algorithm was used here. The minimization assignments were handled by Mark Boise, who was formerly at EORTC and somewhat of an expert on colorectal cancer, so my expectation would be that it was done rigorously and correctly.

Dr. Simon had a disparaging remark to make about that. I think it is probably unlikely, Rich, that investigators at a particular institution would have kept records well enough to anticipate the next assignment or know the exact scheme that was being used.

Furthermore, the only way to gain the assignments

would be to have multiple patients available for assignment at one time, so that you could put forward the patient with the characteristics that you wanted to go on a particular treatment group, and I think that was probably unlikely.

Finally, I would say that probably the issue is immaterial. The times that in the clinical trials' literature where an assignment scheme has been looked at as whether it's important, whether it's simple randomization, blocked and stratified randomization, minimization, or many other techniques, all of the studies have shown that these are all effectively random assuming that the investigators are not gaming, and we don't know whether or not they were, but I think that given the pedigree of how this was done, it is probably very unlikely that there was gaming applied to the treatment assignment.

Thank you.

MR. MOYER: Earlier, your question on informed consent, are you asking whether it was done to U.S. standards as far as collecting--yes, in fact, there is a current audit being performed by the Food and Drug Administration last week, this week, and next week, at several of the centers that participated in this trial to ensure that that was conducted according to U.S. standards.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: Yes. I will try to keep the

question brief. I am very happy to see that so many new trials are being done and particularly adjuvant trials, and it would be nice to see this committee able to approve or recommend approval of a new drug based on a nice adjuvant trial instead of having to struggle with all the things that we deal with, with patients with metastatic disease, but that is just a rhetorical comment.

What I am concerned about, and it hasn't been mentioned so far, is the possibility that the apparent difference and the apparent superiority of the oxaliplatin-containing therapy may be over--what is the word--overemphasized by the fact that the majority of these patients had not received adjuvant 5-FU-based therapy.

If you look at page 17 of the sponsor's packet that they sent us ahead of time, there was an extremely large percentage, two-thirds of the patients who presented with Stage D disease, and similarly, further down on that page, where it says, "prior adjuvant therapy," 80 percent of patients had not received prior adjuvant therapy in both treatment arms, and the same pattern is true for the other study, as well, so I will just restrict my comments to 2962.

So, the first comment has to do with the fact that that non-adjuvant therapy may not reflect what we see commonly in the U.S. in patients with Stage D or metastatic colorectal cancer, and it also seems to be at odds with the

data presented by Mace on page 13 of the new packet that show that the vast majority of patients do not present with metastatic disease and therefore presumably, at least according to common practice in the U.S., a large percentage of patients who would be coming up to a decision of how to treat their metastatic disease will already have had 5-FU-based adjuvant therapy.

Obviously, that question may become moot if it turns out that CPT-11 or oxaliplatin adds so much to adjuvant therapy that we don't have to address it as treatment for metastatic disease, but for now it is a question.

MR. MOYER: So, your question is regarding the number of patients that received adjuvant therapy prior to going on, and actually the limited number--

DR. MARGOLIN: The lack of.

MR. MOYER: --the lack of, the limited number.

Mace, would you like to address that, please.

DR. ROTHENBERG: In looking through the company's briefing document, on page 17 of 88, it has 19.5 percent of people on the control arm and 19.5 percent of people on the experimental arm presenting with Dukes Stage C. That is very close to the 20 percent of patients who had received prior adjuvant chemotherapy.

Now, I should mention that an additional 13.3

percent of patients on both arms presented with Dukes Stage B disease, an area that still remains controversial regarding the routine use of adjuvant chemotherapy.

So, I think that actually, the numbers are quite reflective of both the patient population and also the distribution of these kinds of patients on to Phase III clinical trials of front-line therapy for metastatic cancer, metastatic colorectal cancer where roughly 20 percent of patients do come on after having failed adjuvant therapy.

DR. MARGOLIN: I can't argue with you. I guess the only question would still be the big discrepancy in presenting stages where, on the chart, it's only about 20 percent, but on this page 17 data, it's fully two-thirds of the patients, not that that would necessarily select for people who would have a better difference in the outcomes, but it is just a comment and wonder where all the other patients are with earlier stage diseases when they relapse.

DR. ROTHENBERG: Because on the page that I am looking at, it says 66.2 percent of the control arm and 64.3 percent of the investigational arm presented with Dukes Stage D. So, it was actually the majority of people who went onto this trial actually presented with metastatic disease.

DR. MARGOLIN: Right, which is distinct from the material in the newer document that suggests that only about

20 percent are newly diagnosed with Stage IV, 32,000 out--

DR. ROTHENBERG: In terms of the overall patients who were presenting in the United States each year, only 25 percent, right, but we are selecting from that group, obviously. So, this isn't the group of patients we selected for these trials. These are the group of patients who were diagnosed each year. So, you are right, we are focusing on patients with metastatic disease.

DR. MARGOLIN: I understand. It's just it suggests some kind of a bias in what was seen here versus what actually occurs, that's all, and who was put on this trial versus what is actually out there.

DR. ROTHENBERG: Right, and that would be true of any first-line chemotherapy trial in colorectal cancer for metastatic disease.

DR. SCHILSKY: Thank you. We are going to take a 15-minute break and we will try to reconvene just after 11:20.

[Recess.]

DR. SCHILSKY: I would like to continue with the FDA presentation. Dr. Hirschfeld.

FDA Presentation

DR. HIRSCHFELD: Good morning, Dr. Schilsky, members of the Committee, Drs. Berman, Pazdur, Justice, and my colleagues at the FDA and the NCI, to the press, the

public, those cancer survivors who are here, and patients, the ones who spoke, and to the many who did not have an opportunity to speak, I want to let you know that I share the same goals that you do, and it is particularly fitting that this is colorectal awareness month when we are discussing these applications, and has some personal meaning for me because my stepfather passed away from GI cancer, so I want to let Sam know that I was thinking of him, a little harder than I thought.

I also would like to say bien venue and visiteurs distingues--and I will see how that comes out in the transcript.

[Laughter.]

[Slide.]

We are discussing this morning an application numbered NDA 21063, which is oxaliplatin in combination with 5-FU and leucovorin for first-line therapy for colorectal cancer.

[Slide.]

The regulatory standard for first-line therapy of colorectal cancer is to improve overall survival. That principle has been affirmed many times in discussions by this committee and its predecessors, and in the transcripts of those discussions, particular mention is made that results which are based on tumor measurement, such as

response rate or progression-free survival, are difficult to interpret and we will touch on that theme somewhat later.

[Slide.]

As we have heard, 5-FU plus leucovorin has been the standard of care and will prolong survival compared to 5-FU monotherapy. I would like to in the next few slides share with you based on what is published in the literature what one may expect, so that we can put the results from this morning in context.

[Slide.]

There is no one preferred method of administration of 5-FU/leucovorin. There are many regimens available. On this slide, there is a comparison from over 20 published randomized controlled studies of what one may expect for overall survival for 5-FU/leucovorin using a monthly infusion with low dose leucovorin, about a year; high dose leucovorin, from 8 to 15 months; using the regimen which is often referred to as the Mayo Clinic regimen, from about 10 to 14 months, or the biweekly regimen often referred to as the de Gramont regimen, anywhere from 10 to 15 months.

[Slide.]

There is a lack of correlation and of course any analysis using the literature in any analyses comparing results across studies has disadvantages and weaknesses, but nevertheless, if one asks the question for an individual

study, was there a correlation between response rate and overall survival, these are the results of 23 published controlled studies. From the back of the room, this may appear like a fuzzy cloud, but what this represents is that there is no correlation.

[Slide.]

If one asks the same question for progression-free survival, there is a better clustering, but again it is difficult to make the extrapolation with any degree of certainty between progression-free survival and overall survival.

So, from our point of view, this reinforces the precept, based on the advice we have received from this committee over the years, that overall survival is the critical parameter and measurement of clinical benefit for first-line therapy for patients with colorectal cancer.

[Slide.]

The regulatory history of this NDA is that the studies were designed without prior discussion, so we did not have input into the trial design.

There were meetings, some which were referred to earlier, and one in particular, the FDA affirmed the principle of overall survival, and I will quote, "Approval of any new product in previously untreated advanced colorectal cancer would require demonstration of a survival

advantage," and because are sensitive to the practice of medicine, although we make every attempt not to get involved in the actual practice of medicine, but because we are sensitive to the practices of medicine in the United States, we further stated that the demonstration of a survival advantage when adding oxaliplatin should be to an acceptable U.S.-based 5-FU regimen.

The subsequent meeting with the applicants, we reaffirmed the principles of analysis for survival and stated that for survival analysis, the greatest weight will be placed on the log-rank test.

I would like to state some other general principles before we go into the specifics of this application.

[Slide.]

We will not be discussing whether oxaliplatin has activity against colorectal cancer. We will not be discussing whether the studies that were performed to support this application were high quality studies or not. We feel they were high quality studies.

We will not be discussing whether patients will or will not have access to oxaliplatin. What we will be discussing is the matter at hand, which is, is the claim that the applicant is making that oxaliplatin plus 5-FU/leucovorin should become the first line therapy of choice

in the United States, in other words, the new standard of care for treating patients, that is the issue which we will be discussing.

I will go back one. I meant to call attention here. The sponsor submitted a lot of data to us. There was data on 33 clinical studies, and they provided datasets, complete datasets for 8 studies of which 2 were randomized controlled studies comparing 5-FU/leucovorin to 5-FU/leucovorin plus oxaliplatin in first-line treatment of patients with colorectal cancer.

All the other studies were not controlled studies addressing the question at hand, but were submitted in the form of supportive information, and at this time, I would also like to acknowledge what I personally have felt to be professional, cooperative, and courteous relationships with the sponsor, and in particular I would like to cite Mr. Mark Moyer in our review of this application.

[Slide.]

Study 2961 began enrolling patients in June 1994 and completed its enrollment in March 1996. The primary endpoint specified in the protocol was response rate. The secondary endpoints were progression-free survival, overall survival, and toxicity.

There were two interim analyses planned, and the primary analysis for survival, as stated in the protocol was

the log-rank test. The regimen was based on a chronomodulated schedule.

[Slide.]

The other randomized controlled study in first-line colorectal cancer submitted with this application was Study 2962, which began enrolling patients in August 1995 and completed enrollment in July 1997.

The primary endpoint in this protocol was progression-free survival. Again, overall survival was a secondary endpoint in addition to response rate, tolerance, and quality of life.

There were two interim analyses planned. The primary analysis for survival stated in the protocol again was the log-rank test, and the regimen in this study was a biweekly infusion schedule.

So, again, both studies had different regimens.

[Slide.]

In February 1998, six months after the last patient was enrolled, five months prior to the cut-off date for survival, an amended analysis plan was submitted.

This plan once again affirmed the use of the log-rank test for overall survival and then further stated that a multivariate analysis would be provided using 12 covariates, but these covariates were categories of covariates, some with multiple elements, and they were

defined by terms, such as renal function or liver function, and this amended analysis plan further stated that if other parameters seemed to be pertinent for this analysis, they will be used.

[Slide.]

Having established the principle of overall survival, and having established the preference for the log-rank test as a means to determine overall survival in an unadjusted manner, here are the results of the two randomized controlled studies that were submitted.

Study 2961 showed in the control arm a median survival of 19.2 months, and in the oxaliplatin-containing arm, a median survival of 17.4 months, or to put it in another way, approximately a two-month deficit for those patients who received oxaliplatin. The log-rank test was 0.58 and I think what one can conclude from this is there was probably no difference between the study arms.

The second study in the control arm showed a median survival of 14.7 months; in the oxaliplatin arm, 15.9 months, or in other words, a one-month difference approximately, and the log-rank test was 0.135, which is the same numbers which the sponsor calculated. So, we agree with this analysis and with the calculations which were performed to achieve these results.

There was some discussion earlier this morning of

response rate, and although I do not wish to emphasize response rate as indicative of, or predictive of, results in first-line therapy for colorectal cancer, we tend to look with interest at what are called complete responses, that is, those responses which are in patients which have detectable tumor and then at some point during their therapy, they have no detectable tumor within the sensitivity of the instruments being used to measure tumor, and they remain without detectable tumor for typically at least four weeks.

If we look at the complete response rate in the arms of these two studies, we find that the complete response rate in Study 2961, which was the chronomodulated study, there were no patients that achieved a complete response, and in the oxaliplatin, there was one patient that achieved a complete response.

If we look at the complete response rates in 2962, which used a different, the biweekly infusion schedule, the complete response rate in the control arm was one patient, and if we look in the oxaliplatin-containing arm, the complete response rate was three patients. These numbers are too small to analyze, but don't seem to indicate a difference.

[Slide.]

You have seen these curves before--in prettier

colors I might add--but this is the Kaplan-Meier survival curve for Study 2961, and the oxaliplatin-containing arm is this blue one, which I am tracing with some difficulty, and the control arm is the brown one.

[Slide.]

The same color scheme holds up here for Study 2962. The blue arm represents the oxaliplatin, and the brown represents the control arm.

We are also struck by the similarity of the curves.

[Slide.]

The criteria fundamentally for approval of a claim--and I want to emphasize again it's a claim, it is not an agent--is that there is some demonstration of clinical benefit, so we examined whether there was clinical benefit other than analysis of survival which we will address again, which were seen in these studies.

Clinical benefit assessments were scheduled and were part of the protocol of Study 2962, and some of the criteria were performance status, pain scores, weight change, symptom improvement or quality of life, and as has been noted, compliance with the questionnaire for quality of life and the measurements in each of these parameters are not as robust as one may hope for, but there was no demonstration of difference in any of these parameters

between the study arms.

[Slide.]

I would like to show you something you have not seen yet this morning, and this is the scope of adverse events, of total adverse events, not just adverse events which are Grade 3 and 4.

The yellow here represents all adverse events for oxaliplatin, and these categories are diarrhea, nausea and vomiting, thrombocytopenia, neutropenia, leukopenia, and paresthesia. You can see in each of these categories there were differences, sometimes large, as to patients that experienced these adverse events.

The light green represents the serious or Grade 4 adverse events, and to interpret this, this says, for instance, that 42 percent of the patients had serious Grade 4 diarrhea, approximately 25 percent nausea and vomiting, and approximately 42 percent had the paresthesias.

The grading of neurosensory or neurological complications was different in each of the studies. There was more precision in Study 2962, which I will show you in a moment, compared to 2962. So, we don't have an idea of the scope or range or implications in this adverse event grading as we will in the next study.

The control, just to identify, is all the adverse events is the light purple, and the serious adverse events

are the red.

[Slide.]

Examining the adverse event profile for Study 2962, we find again that fever without infection, stomatitis, diarrhea, vomiting, nausea, thrombocytopenia, neutropenia, leukopenia, and neurosensory all exhibited large differences between the total number of adverse events in the control arm and in the oxaliplatin-containing arm, and the same qualitative sense was seen in the serious adverse events.

[Slide.]

The neurotoxicity was graded using a scale prior to the revisions of the National Cancer Institute Common Toxicity Criteria Version 2. The scale that is represented in the protocol has Grade 1 as the event resolved by the next cycle; Grade 2, that the event persisted between cycles; and Grade 3, that there was permanent impairment. So, anything marked Grade 3 has to be interpreted as having permanent impairment.

We see here that 17 percent of the patients were graded as Grade 3 or having some permanent impairment, and I don't have a slide to show you, but I will refresh some of the numbers which were discussed earlier.

With regard to laryngospasm, 1 percent of the patients on the oxaliplatin arm experienced what was

considered severe laryngospasm. Approximately 8 percent of the patients had cramps compared to 1 percent on the control arm.

For pharyngolaryngeal dysthesias, there was one patient on the control arm and 22 percent, or 47 patients, on the oxaliplatin-containing arm, of which one was considered to have permanent impairment.

Lastly, there is a sign which is often a board question in oncology, that is, Lhermitte's sign. What is Lhermitte's sign? The correct answer--and my final answer will be--that it's if you turn your head, twist your neck, you will get sensations like electric shocks moving up and down the spine. Seven patients, or 3 percent, of the patients in the oxaliplatin-containing arm were described as experiencing Lhermitte's sign.

[Slide.]

What you didn't see earlier was the curve for cumulative neurotoxicity of all grades. This is the curve for Grade 3, which again is the permanent impairment grade. This is Grade 2, and the scale here is somewhat different. It doesn't show you cycles. It shows you the cumulative dose.

This is the grade it may be very difficult to see for Grade 2, which is those events which persist between cycles, and this is the Grade 1, which starts essentially at

the very first dose.

We can see that it is highly probable that at least 80 percent of the patients will experience a minimum of Grade 1 and that approximately 20 percent will experience a Grade 3, which is the permanent impairment.

[Slide.]

That is all the data that I will share with you now, and I wanted to then discuss what I consider some of the strengths and weaknesses of this application.

There were randomized, controlled, multi-center studies, and this is not to be minimized. These studies are difficult to perform. It requires coordination. They were in many countries, and we applaud the effort of the investigators who initiated, conducted, and finished these studies, because the oncology literature is replete with incomplete studies.

[Slide.]

There were several weaknesses, and our interpretation of weakness is just that, our interpretation, but we felt that the survival results that were presented were consistent with those that one may see with 5-FU/leucovorin alone. In other words, the month advantage that was seen in survival between the study arms could be within the parameters of the range of what one sees in published studies with 5-FU/leucovorin alone.

In addition, we felt that the reliance on an adjusted analysis to demonstrate efficacy was a weakness, and it was a weakness for a number of reasons, but one was the large number of covariates, and the second was--and I anticipate that this will be a topic for discussion later on--the selection of the covariates in the statistical model that was dependent upon study outcome.

There was presented earlier this morning, but which we chose not to address, and that is an analysis which is based on secondary therapy.

I should also add that although there were citations made to the literature with regard to the validity of the alkaline phosphatase marker, the complete search of the literature reveals that there are many potential prognostic markers, and there are studies that support alkaline phosphatase and studies that do not support alkaline phosphatase, and these have been examined since at least 1985, and the acceptance of alkaline phosphatase as a prognostic marker in first-line colorectal therapy trials has not been universal, and as far as we are aware, based on the submissions that we see, it is not a standard prospective stratification.

[Slide.]

Another weakness was the lack of basis for extrapolation to 5-FU/leucovorin regimens used in the United

States. One may say why was there a difference in outcome of the two studies in this trial.

One interpretation is that they weren't any different, they were both equivocal. Another interpretation, which you have heard earlier today, is that one of the studies demonstrated a survival benefit while the other didn't. That begs the question what could the explanation be - could it be because different regimens give different results?

Another difficulty is that the schedule of 5-FU/leucovorin, while generally analyses of published studies show that survival is approximately the same, the outcome in terms of adverse events and risk/benefit ratio varies highly among different regimens, which is the impetus for developing some of the regimens which Professor de Gramont and Professor Levi did in order to address this risk/benefit ratio in terms of the serious events.

There is greater toxicity on the oxaliplatin arm, particularly neurotoxicity with oxaliplatin-containing regimens, and we have concerns about the applicability of these oxaliplatin regimens which were different in the two studies to a regimen which may occur in the United States.

We also feel that cross-study comparisons or exploratory analyses should not form the basis for approval for an indication as important as first-line therapy for

colorectal cancer.

[Slide.]

I would like to address, since it was referred to, some of the principles enunciated in the FDA Guidance on Providing Clinical Evidence of Effectiveness which was published in 1998.

One of the principles is that there should be substantiation of results. "A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion for effectiveness."

Furthermore, "Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study"--or I may add an adjusted analysis--"will lead to an erroneous conclusion that a treatment is effective."

[Slide.]

It further states that, "a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use."

[Slide.]

And that, "Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was

in error"--again, this is not a comment stating that one study was favorable and the other was not favorable, this is just a statement of principle from the FDA guidance--"it is often reason not to rely on the single favorable study."

[Slide.]

So, what would be the criteria for submitting a single study? The criteria should be that the findings are clinically important, that the study should have a "statistically very persuasive finding" and that "confirmation of the result in a second trial would be practically or ethically impossible."

[Slide.]

With regard to the principles which have been in effect at the FDA and have been also adopted by the ICH, the International Conference on Harmonization, with regard to multivariate analysis, the principles state that, "Pre-study deliberations should identify those covariates."

Further, "When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as one for primary attention, the adjusted analysis being supportive."

[Slide.]

These are the principles which we have adhered to in the review of this application. I am just the fortunate individual that can communicate the results of our analysis

to you, but there was an entire team of colleagues, and they are all listed on this slide, but particularly, I would like to recognize our colleagues in Biometrics, Drs. Mark Rothmann and Gang Chen; my colleagues in the Clinical Review, Drs. Nagamura, Johnson, and Justice; and the contribution, often unheralded, of our project manager staff, which in this case was Christy Wilson and her supervisor, Dotti Pease.

At this point, I and all of my colleagues would be ready to entertain any questions.

Thank you.

Questions from the Committee

DR. SCHILSKY: Thank you very much, Steve.

Steve, let me take the Chair's prerogative and just ask you for clarification on one point and then we will certainly open it up for discussion.

In your slide showing the regulatory history, there was a comment made that in 1996, the agency stated that "Approval of a new product in previously untreated advanced colorectal cancer would require demonstration of a survival advantage when adding oxaliplatin to an acceptable U.S.-based 5-FU regimen."

I am wondering if you could elaborate a little bit further on the reason for specifying an acceptable U.S.-based 5-FU regimen.

Is it related to just, as you mentioned, being sensitive to the practice styles in the U.S., were there other concerns involved?

Clearly, the sponsor chose not to present such information at least today, and obviously, if the drug were available and marketed in the United States, my understanding is that although the FDA might control how the drug is promoted, it wouldn't necessarily be able to control how the drug is actually used by practicing oncologists.

So, I wonder if you could elaborate further on the concerns that the agency might have about the importance of the U.S.-based regimen.

DR. HIRSCHFELD: Well, Dr. Schilsky, you have touched on some of the concerns, and that is that it is unlikely that the regimens that were used in these studies would be used in the United States for a variety of reasons, but our concerns were that given the diversity of profiles seen both for benefit and risk in 5-FU-containing regimens, that we, since our obligation is to provide accurate information, and to attempt to maximize the benefits that any therapy could have through the use of information, our concern was that we would provide information which would be consistent with the way the product would most likely be used, which is not to say that the product has no use or that the product may have applications in other settings,

but given the claim that was being proposed, we were concerned that the applicability or the extrapolatability of not only the efficacy data, but more particularly the adverse event data would be uninformative, and that we would be exposing patients to a risk or physicians to a risk which, if we had the opportunity to avoid, we would avoid it.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: I don't know if you can go back to your very first slide now that the computer is off, but one of the first slides you showed was that the bar for approval for a new agent in colorectal cancer was set as a survival advantage as first-line therapy.

That is a very difficult disease, colorectal cancer, and for a long time that was undoubtedly true. I wonder whether that paradigm is correct and if you can get the slide up, it might be helpful.

There are at least two new drugs, one of which we are talking about now, one of which we will talk about this afternoon, that clearly are active in this disease, that change response rates, and we will hear about survival this afternoon.

Under what circumstances in a disease is it appropriate to begin to shift from requiring a survival advantage in first-line therapy as new effective second-line

treatments are developed, and to look at other endpoints, such as time of progression, are there models for that in other tumors, and is it time that we should consider shifting our model in colorectal cancer from a requirement for first therapy of survival to another endpoint?

DR. HIRSCHFELD: I will read the text of the slide, Dr. Kelsen. It's the regulatory standard for first line therapy of colorectal is to improve overall survival. Philosophically, the FDA has I believe always, but certainly now, is open to whatever analyses and whatever trial design would show the most informative studies in a particular disease context, and the principles are generally, and in this particular case, have been enunciated in discussions with and on the advice of the Oncology Advisory Committee.

We had a discussion on a different disease last year, in June of 1999, on breast cancer where again the issue was whether survival should be the regulatory standard for approval for first-line therapy, and the committee rather strongly supported that point of view, and in addition, it supported the point of view with the recognition that it was not necessarily restricted just to breast cancer, but would apply to other disease settings.

DR. KELSEN: It will become increasingly difficult as we identify new treatments in this disease, and just talking about colorectal cancer, because I believe we have,

and particularly as we begin to salvage patients who have previously unresectable liver metastasis, since that is a very common pattern in this disease as distinct from perhaps other solid tumors, and it will further and further muddy the waters of trying to bring important new therapies to the general population if we continue to ask for survival only, and I raise that as a point of discussion.

DR. SCHILSKY: Perhaps we can defer that to the discussion portion and just entertain questions right now that focus specifically on Dr. Hirschfeld's presentation.

Ms. Forman.

MS. FORMAN: When a sponsor asks for an amended analysis or presents an amended analysis, as this sponsor has done, does that require FDA approval?

DR. HIRSCHFELD: The only approvals which we formally grant are marketing licenses, and if the question is did the sponsor get concurrence on the amended analysis, I can only--I was not at the meeting--I can only reconstruct from the meeting minutes, but there was discussion, and the understanding that the agency had was that despite the intent to use amended analyses and multivariate analyses, that the primary analysis of survival, as well as progression-free survival, would still be based on the log-rank test.

So, in general, the question is that we appreciate

being informed of changes in analyses, but we don't necessarily have to concur for that analysis to proceed.

I think it is testimony to our flexibility that we are bringing this application to this committee and asking for advice rather than categorically making a unilateral decision.

DR. SCHILSKY: Other questions from the committee members? Dr. Lippman.

DR. LIPPMAN: This is sort of to clarify what we will discuss later on David's point.

When you look at the slide on the top of page 3, on the correlation between response rate and overall survival, the 23 studies, and presumably, most of those studies were before there were active second-line therapies, and still there is no correlation in response, between response and survival.

If you look at maybe the more recent slide, more recent studies that may have been done when there were active second-line therapies, is there a better correlation between response and survival?

DR. HIRSCHFELD: The answer is we didn't--it is always difficult to do this type of analysis. I will just state that at the onset. We decided to be more encompassing than restrictive in looking at the studies, but if we had, let's say, picked some landmark like we will say 1992 or

some other date, and looked at before and after, we didn't find any differences.

That doesn't mean it doesn't exist, but it is not something that could be demonstrated readily or something that I think could be considered persuasive in terms of evidence-based medicine.

DR. SCHILSKY: Steve, let me ask another question. You showed us a slide and which you summarized clinical benefit assessments, and you said that the agency agrees with the sponsor's analysis that there were no statistically significant differences in a number of parameters, performance status, pain, weight change, and so on.

So, having done that analysis and having agreed with the sponsor that there were no significant differences, do you consider that to be a strength or a weakness of the application?

DR. HIRSCHFELD: I will only speak for myself. I have a fair degree of skepticism with these types of endpoints and particularly when the compliance with the measurements is less than robust, so I would say that whether it's a strength or a weakness, I would feel neutral about this actually, and I am neutral because I recognize the challenge in collecting and interpreting these data.

DR. SCHILSKY: I guess the reason I asked the question is because I have some concern that there may be a

sense that the absence of a decrement in quality of life would be interpreted as a benefit to patients as opposed to an improvement in their quality of life.

DR. HIRSCHFELD: We share the same concern, but absent robust data, all we can do is state our concern.

DR. SCHILSKY: Other questions from the committee?

DR. HIRSCHFELD: So, just to paraphrase, I think your concern and our concern, just because no difference was noted in an analysis, it doesn't mean that there are no differences, and it doesn't mean that the quality of life or patient benefit is necessarily the same.

DR. SCHILSKY: I agree.

Dr. Lippman.

DR. LIPPMAN: Just one last thing. Since a major issue regarding the survival is the adjusted analysis and the impact of alkaline phosphatase, did you look at those data? Were they available for the second trial to see if one controls for alkaline phosphatase, if the results change?

DR. HIRSCHFELD: I am going to call on my colleague, Dr. Mark Rothmann. The answer is yes, we did, but I think Mark invested enough time and effort that he deserves at least a chance to state his point of view.

DR. ROTHMANN: Mark Rothmann, Statistics Review, FDA. I guess the best answer I can give, we didn't look at

just adjusting for that factor in the other study, but adjusting for a variety of factors as did the sponsor submit something those lines, and it did not change the results. The smallest p-value we got--and we did two of these--was like 0.49.

DR. SCHILSKY: If there are no other questions for Dr. Hirschfeld, thank you. Dr. Albain?

DR. ALBAIN: Yes, sorry.

DR. SCHILSKY: A question just came to mind?

DR. ALBAIN: Yes. It was on the same subject. I look at the multivariate modeling as a strength here, not a weakness, and I do so because it seems as though when you control for not just alkaline phosphatase, but other univariate predictors in your model appropriately, you still have a strong treatment effect, and, in fact stronger.

To me, that is an appropriate thing to do in a large Phase III trial, and I wondered if you could clarify why you felt that to be a weakness.

DR. HIRSCHFELD: I will begin the answer, and I will again call on Dr. Rothmann to complete, but what we got was a packet with multiple analyses in them, and it wasn't clear to us why one analysis was chosen over another one other than the fact it gave a particular outcome.

So, from our perception--and it may be our weakness, I am willing to admit that--but from our

perception, when we were confronted with multiple analyses using multiple models, we felt that this was potentially obscuring effect or making it difficult to interpret the reliability of any particular analysis.

DR. ROTHMANN: It is hard to interpret analyses for which have covariants, that you don't know whether or not they are going to appear in the model, they are not prespecified as appearing in the model. Had they been, then, there wouldn't be any sort of adjustment for possibility of Type 1 error, but sort of an issue, somewhat of an issue is do you make adjustments because the treatment arm was like the fourth factor that made it to the model.

Another issue, I guess, that Steve mentioned, baseline alkaline phosphatase was not even really prespecified in their statistical analysis plan, just liver function tests.

DR. SCHILSKY: Dr. Simon.

DR. SIMON: Can you specify what the widely accepted prognostic factors for advanced colorectal cancer are, the major ones, and did you do an adjusted analysis of Study 62, adjusting only for those factors?

DR. HIRSCHFELD: We had an internal discussion as to what the most widely accepted prognostic factors are, and I can tell you that we entertained factors such as performance status, which is considered a widely accepted

prognostic factor, extent of disease varies by chemical parameters, age of patient, whether the disease was just in the rectum or whether it was colon and rectum. These were part of the universe which we examined, and CEA antigen.

The difficulty--and I am starting to think of more--number of liver metastases that can be counted, and all of these have been supported in one way or another by some segment of the literature, and we explored all of these, but didn't have confidence in any one particular model over another one.

I don't know if you would like to add something more? No, okay. So, that will be our final answer.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: On that same issue, I didn't realize this until the FDA presentation, but although the covariate analysis was prespecified, it was prespecified fairly late in the trial according to your page 6 slide.

When that came to you, what were the reasons for adding the adjustment for covariate five months prior to the cut-off date?

DR. HIRSCHFELD: I am not sure I am understanding the question.

DR. LIPPMAN: Well, it was amended in February of 1998 to include that.

DR. HIRSCHFELD: Correct.

DR. LIPPMAN: What were the reasons for putting that in at the time, were some of these prognostic factors becoming available or better known at that point?

DR. HIRSCHFELD: Why was the amended analysis plan submitted? I think at that point in the study there had already been two interim analyses and I wouldn't want to speculate, so I may have to turn the question back to the sponsor as to why they chose to submit the amended analyses at that point in the study program.

MR. MOYER: The answer is regarding the protocol. If you can turn to page 16 of the sponsor's document, you will read the wording in the first paragraph which says specifically, the protocol for ESC 2962 stated that overall survival--and this is a quote--"will be compared between the two treatment arms using the log-rank test. Further explanatory analyses will be performed to adjust the treatment comparison for accidental bias in using multivariate models. Proportional hazard models will include predictive estimates, prognostic factors, and inclusion, such as performance status. Such analyses will complement but not replace the unadjusted analyses."

Now, when we met with the FDA in '96, it was actually October and November of '96, prior to the analysis for survival, we went in and we were discussing this survival with the endpoint of progression-free survival

being the primary endpoint.

FDA at that time asked us to submit the plan for survival analysis because that was the secondary endpoint, which was submitted in February--actually, '97, I am sorry, it was '97 that we met with them.

We had an October meeting in which, yes, we did get told about the use of the U.S. regimen of which actually in October '97, went back to the agency because we had also found a bridging study with this French intergroup trial that enabled us to demonstrate consistency of the Mayo regimen with the 5-FU regimen done by Dr. de Gramont, and at that time, in '97, October '97, we discussed the survival analysis, and that was submitted in February of '98, right after that meeting.

DR. SCHILSKY: Thank you for clarifying that. My interpretation of the quote you just read us from the protocol is that the adjusted analyses would not replace the primary unadjusted analyses.

MR. MOYER: That's correct.

DR. SCHILSKY: So, we should focus then on the unadjusted analyses. Thank you.

Dr. Margolin.

DR. MARGOLIN : Again, another just very small statistically oriented question. I am not sure that you actually did the interim analyses, but if you did, did you

not have to adjust the final p-value of what was then going to be this non-adjusted final analysis to compensate for the interim--

MR. MOYER: I will let my statisticians discuss that specifically, but the first was a stopping rule for response rate, and the second interim analysis was also for response rate, and which that was done, so it was very early on that that interim analysis was performed, and we did not look at survival at that point in time.

DR. MARGOLIN: So, in the study that--well, you gave us response rates in both studies. Do the p-values that are felt to be significant there, are those in accordance with the p-values that you agreed upon based on the two interim analyses for response rates?

MR. MOYER: Yes.

DR. SCHILSKY: Let's keep the questions focused on the FDA presentation. We have already had an opportunity to question the sponsor.

Other questions from the committee?

[No response.]

DR. HIRSCHFELD: I thank you then.

DR. SCHILSKY: Thank you.

Committee Discussion and Vote

DR. SCHILSKY: We have an opportunity for general discussion among the committee members. We also have some

questions posed to us by FDA that we will need to focus on and answer.

I am wondering if anyone around the table would like to make any general comments at this point before we focus on the questions.

Dr. Simon.

DR. SIMON: I just wanted to clarify some of the points I made before. There are basically four statistical issues here that are of some concern to me. The one was the one I mentioned originally, is this data mature enough for analysis.

At least in the submission, there were about 170 cases that were censored from the survival analysis, and we are sort of struggling to understand is there a significant survival effect or isn't there, and do we adjust or don't we adjust, and the simplest way of trying to clarify that is to have very updated data, the most updated data in the survival analysis, and to have the data presented that is essentially a year and a half old, with all those patients censored from the analysis, I don't think is optimal. So, I view that as a limitation.

The second issue was the issue of the minimization. There are a whole variety of stratification methods that are used in clinical trials, some of them I call adaptive stratification methods, and all but one of

them have the characteristic that they keep a certain randomness in the treatment assignment process.

They keep the randomness in for a variety of reasons, but one of the reasons is to keep the people entering the patients from being able to predict what the next treatment assignment is, and that is really the most critical role of randomization.

The one method that does not keep that randomness is minimization. Although various kinds of stratifications are used by U.S. cancer cooperative groups, I am not aware that any of them use minimization with no random component in it.

Now, they use only three stratification variables in this minimization. One was center, one was performance status in which they grouped the zeros and 1's, and which constituted 90 percent of the patients. So, it is essentially not even a stratification factor for this minimization. The third one was number of sites.

So, I, in contrast to what Dr. Piantadosi says, I believe there was at small centers a significant potential for being able to predict what the next treatment assignment was without anything going to any great lengths to keep track of what the treatment assignments were.

That may very well not have happened, but I view it as a limitation of the study.

DR. SCHILSKY: Can I just ask you to elaborate further. Your concern would be that if such a potential existed that a physician might determine that a patient with a particular set of characteristics might be offered participation in a study at a particular point in time, with the expectation that they would get one arm or the other?

DR. SIMON: Right, but if you know that the next treatment assignment is not going to include oxaliplatin, then, you may decide not to enter, to withhold your patient and not enter the patient.

I mean I don't know that that is a big deal, but I think it is a defect in the study conduct.

The third issue is the issue of adjustment for prognostic factors. I don't think the issue is should one adjust for prognostic factors or shouldn't one adjust for prognostic factors.

I think if you have very strong prognostic factors, it's a good idea to adjust for them, but I think you really need to specify which prognostic factors you are going to adjust for in the protocol, because otherwise you get into what we here have gotten into, the subjectivity of which ones you adjust for and whether the method picked for selecting those ones introduces a bias or using stepwise regression the way it is described in the submission to decide which ones to adjust for, leaves the p-value

associated with the treatment effect not the normal kind of p-value that we are used to. It's not really a p-value of a prespecified hypothesis test.

So, I think it is good to adjust for prognostic factors, but you need to specify in the protocol what those prognostic factors will be and you need to adjust then for all of them that are specified in the protocol.

The final issue of concern to me, the analysis that we are presented in which patients were censored when they went on to a second-line treatment, I view as sort of totally invalid.

One of the basic assumptions of the Kaplan-Meier calculation and of the log-rank test is that there is no what is called informative censoring, and by censoring patients when they go on to either secondary treatment, it indicates they have progressed, it indicates maybe--who knows what it indicates, but it is very likely to be informative censoring and to violate the assumptions of those analyses.

DR. SCHILSKY: Thank you.

I am wondering if any of the committee members want to discuss at all the issue of the 5-FU regimen used. One of the things that struck me, I must say, in thinking about this is looking back at the publication of what the sponsor is referring to as the intergroup study, the

bridging study. Now, that was published in 1997.

That study in the publication did demonstrate a greater response rate and progression-free survival compared with a standard U.S.-based regimen. Yet, it is not obvious to me as a clinical oncologist that many U.S. oncologists have accepted the de Gramont regimen despite the fact that that paper was published two-plus years ago.

Furthermore, I have some concerns about the notion that that study, of course, did not demonstrate a survival advantage for that 5-FU-based regimen, and one might argue that it is a regimen that is perhaps somewhat more cumbersome to administer than the usual 5-FU bolus regimens that are commonly used in this country.

So, we are sort of in a situation where we have a 5-FU regimen which does not provide a survival advantage over U.S. conventionally used regimens. That is perhaps somewhat more cumbersome to administer. Now we add another drug to that regimen again without showing any further survival advantage and adding a new set of toxicities.

So, where have we come over this period of time with a changing of 5-FU regimen and adding a new drug? It seems to me that we are not clearly further down the road in terms of benefitting patients except that we have now devised a regimen that is technically more complex to administer and has a new set of toxicities compared to the

U.S.-based conventional bolus regimens.

That is a personal view. I don't know if other members of the committee share that view or anyone else would wish to comment.

Kim?

DR. MARGOLIN: Well, I think that the main advantage of the selection of that regimen and using the information from that intergroup trial to design this regimen was a safety one rather than an efficacy one.

I think what we saw was to reassure us that the regimen was not inferior to the regimens we tend to use here, and it seemed to be substantially less toxic in some of the dose-limiting toxicities, thus allowing the safe addition of the selected dose and schedule of the oxaliplatin, so again back to the issue of if we were to approve this, we would have to approve it with very, very narrow kinds of guidelines on how it is to be used, and then can't control what happens once it gets out.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: Just from the technical point of view of giving 5-FU by infusion, I think 5-FU infusions are widely used in the United States with radiation, without radiation therapy, with programmable pumps, without programmable pumps, through metaports, through PICC lines, so I would guess that most oncologists are reasonably

comfortable with giving 5-FU by an infusion, and Dr. de Gramont's regimen is a variation on that. I don't think the technical aspects are the problem.

DR. SCHILSKY: Do you have any views as to why that regimen has not been more widely used in the U.S.?

DR. KELSEN: I think that actually, a number of oncologists in the U.S. are beginning to use it more frequently. Why was it chosen, why do we give it for 14 days, and then seven days, and 21 days, I mean it is just practice style. I mean there are people who will give radiation for rectal cancer, and they will give a 5-FU infusion for six weeks without blinking an eye.

DR. SCHILSKY: Other general comments or points of discussion?

MR. MOYER: Is it possible for Dr. Piantadosi to discuss the design of the study? It seems to me there is a difference in opinions with that.

DR. SCHILSKY: It is my understanding that Dr. Piantadosi was not involved in the design of the study, so I don't really see a need for him to discuss it with us.

DR. KELSEN: Can I get back to the question I asked at the beginning?

DR. SCHILSKY: Please.

DR. KELSEN: I mean this is a difficult disease, as I said before, but I do think that there is progress been

made over the last few years. We have identified irinotecan as an active drug.

I don't know the other committee members' feelings, but I think the data that this oxaliplatin is an active agent in this disease is very persuasive. It clearly causes regressions both in first-line and second-line therapy, and its safety profile, I think has been pretty well established.

The issue I am grappling with is the slide that Steve showed, No. 1, which is that the bar is an improvement in survival as first-line therapy, and one has to clearly demonstrate that outcome.

I really hope that over the next few years it will be harder and harder, as we have better and better drugs, to identify that, and there is something a little funny about colorectal cancer, it's a little different than a lot of other solid tumors.

Surgical salvage is possible in a small but defined fraction of patients, and that salvage is curative therapy, and there are not many solid tumors--maybe sarcoma with lung metastasis--in which we intervene routinely and safely, resect hepatic metastasis and cure a small but defined percentage of patients.

That will further muddy the waters. It might be a little different than breast cancer. So, I again wonder if

the appropriate endpoint should remain survival, which might become a harder and harder thing to show, and we might miss an important new drug, and whether there is a model--and I am asking, I don't know--if there is a model for when one begins to switch to another endpoint, and a time to tumor progression seems a reasonable one to me. I am not in favor of response, but time to tumor progression might be an acceptable alternative.

DR. SCHILSKY: David, before we discuss that further, let me just remind you I think Dr. Hirschfeld made a very important point that we, as a committee, should keep in mind, and that the issue before us is not whether this drug has activity in treatment of patients with colorectal cancer.

The issue really is the fundamental claim by the sponsor that this drug, in combination with a particular way of giving 5-FU and leucovorin, should become accepted as the new standard of care for first-line therapy of patients with metastatic disease based upon the data that have been presented.

DR. KELSEN: I agree with that and accept that. I am wondering if the measure of efficacy, put response to the side, if the surrogate for efficacy, the measure of efficacy rather is a change in outcome measured by a change in time to tumor progression, which is a difference in outcome over

time rather than just it got a little smaller for a month.

DR. SCHILSKY: Dr. Sledge, Dr. Johnson, Dr. Nerenstone.

DR. SLEDGE: I think that is a concern many of us share for many diseases. I certainly share that concern for breast cancer. However, I have got to say I don't particularly share it for this particular drug, because the problem is not that the patient is going on this trial that had three prior chemotherapies, and therefore it made too high a bar to jump over.

This, in fact, was a trial where 80 percent of the patients had had no prior chemotherapy, so it doesn't strike me as a particularly startlingly high bar to jump over from that standpoint.

DR. D. JOHNSON: I will not address the particulars of this, but the issue that you raised regarding the increased use of salvage therapy. First of all, I don't think that that is new. It has been around for a long time. Certainly, drugs have been used as second-line therapy.

You can argue that the drugs we are dealing with today are, quote, unquote, "more active" than some of the drugs that we have had in the past, and I would personally agree with that. Some people might differ with us on that issue.

I guess I would feel that way if, for example, in

this trial, as an example, not specifically related to this trial, it is not as if one group got salvaged and the other did not. In fact, as I looked at these data, they showed exactly the same number of patients got salvaged.

Then, you are postulating that the salvaging drug on the control arm is superior to the salvaging drug on the experimental arm. In this case, there were two drugs that were active - CPT-11 presumably, that has been already approved for such, and oxaliplatin.

My view is that they balance out anyway, so therefore they should have been, if there was an advantage at all for upfront oxaliplatin, again just using this as an example, not as an argument for approving or disapproving, it seems to me that the survival advantage would have survived.

The example that exists, in my mind, is Herceptin, and I think there it is fairly clear that giving Herceptin to those patients second line, who were on the control arm, had an impact, but it did not impact the overall survival using it upfront.

It also sort of goes against some of the tenets of what I understand regarding chemotherapy usage, giving it early versus giving it late. If you have got ineffective drugs, it makes no difference. If you have effective drugs, it ought to make a difference where one gives those

therapies.

The last comment I would make is that I personally think time to progression is a horrible endpoint as we do it today. If we, in fact, use that as a surrogate--and we made these arguments a year ago--we are going to have to redefine how we determine that endpoint.

There are plenty of examples that I can think of, at least in some diseases like lung cancer, where second-line therapy really has not had an impact when one compares it against supportive care in that setting.

To me, that is what we need before we move to the next step that you are proposing, David, which I happen to agree with you philosophically, but what I would like to see is a random trial where, in fact, supportive care was given as second-line, comparing it to the best possible therapy.

We have that with CPT-11, we don't have that yet with a lot of other drugs, and therefore I think one could argue that CPT-11 might have impacted survival, but I am not sure you can now argue that oxaliplatin has that.

So, it is a very complex issue, but I personally find it very difficult to use it, and I believe that if there is a sufficient clinically relevant survival advantage, it will emerge ultimately, because these patients will end up randomly getting equally poor or equally good, quote, "salvage" therapy.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: Most of my comments have been stated. I think the other problem about time to tumor progression, which again came up in our other discussions, is that it is extremely subjective, and in these studies which are not blinded, when you decide that somebody is progressing on treatment, is very much biased by the investigator who may know that somebody is getting an experimental drug versus not getting an experimental drug, so I think time to progression per se is a very poor indicator.

I just have sort of a general comment, then, and I sort of need to probably throw it back to the FDA. As a clinician, I sat through this presentation and felt extremely frustrated, because we certainly need new drugs for colon cancer, and I think that with the data that have been presented in some of the ancillary studies and some of the other things and from personal experience of having some of my patients go on study, on some of these kinds of studies, feel that this is an active drug.

I don't think, however, that this application has proven for the indication that has come up. So, my question to the FDA is, is there something short of approval in this setting that we can do or are we limited to a yes or no vote on this indication, period?

DR. JUSTICE: Are you asking whether accelerated approval is an option in this case? No, I don't think so, because there are alternative therapies.

DR. NERENSTONE: Even for third-line, second- or third-line treatment? Not first-line, but second- or third-line?

DR. JUSTICE: Well, second-line would not be because CPT-11 is approved for second-line, so, third-line, could they do a study showing that patients who were refractory to first- and second-line, then, get a reasonable response rate in third-line, that's a possibility. You know, generally, response rate in that setting are very low, and it is not necessarily the route we would recommend.

DR. HIRSCHFELD: I would just comment that I share that feeling, and we are in a position where we say, boy, if only this were part of it or if only that were part of it, then, we could perform our functions, and we would do it expeditiously.

I remember there was a comment earlier today about accelerating the review, and we try to accelerate every review, and I think our time standards are getting better all the time. Part of that has to do with the increasing sophistication of having data come in electronically, but we share that position, but we are restricted by both federal regulation, the claim that is being made, and the data that

is used to support that claim.

DR. D. JOHNSON: May I make one last point, by the way, that deals with the time to progression issue and the progression-free survival.

It is particularly problematic in my mind. When the investigators know that when the patient progresses, they get to go on to the, quote, unquote, "new" drug. I mean that is a huge problem.

So, little dits along the chest x-ray that you might suggest is scarring if you think it's oxaliplatin or whatever other drug you are looking at, rhubarb pie, versus, you know, that's a new met if you are on the control arm. I mean that is what really perturbs, in my view, those types of analyses, and it has nothing to do with statistics, it just has to do with what we, as physicians, want to do for our patients. It's a bias that we can't get away from.

DR. BERMAN: Dr. Schilsky, could I add something to what Dr. Nerenstone asked?

DR. SCHILSKY: Please.

DR. BERMAN: It touches also on the bar, the hurdle, because there is nothing in the Food, Drug, and Cosmetic Act or in the regulations that requires survival. What we need is demonstration of clinical benefit.

Just from the brief discussion that has just occurred, it sounds like time to progression in this case,

the committee is not going to conclude as evidence of time of clinical benefit.

The only way there would be a opportunity for an approval is if you believe this application supports a clinical benefit. You could give us the feedback that you don't think survival was necessary to support clinical benefit. In fact, Steve was quoting this committee when he talked about the hurdle and the bar and our following your advice, but there would have to be something in the application you thought represented convincingly clinical benefit.

DR. HIRSCHFELD: May I just add that clinical benefit is not necessarily solely defined in terms of efficacy, but we would consider less toxicity or perhaps even a different dosage form that may be easier to administer. Those all could be considered clinical benefit.

DR. SCHILSKY: I think if I could just very briefly summarize this time to progression discussion, because we have had it on many occasions in this committee.

My sense is that most of the committee members, at least philosophically would view time to progression in some circumstances as being an appropriate endpoint in a clinical trial.

The real issue, though, is the rigor with which time to progression is assessed in terms of whether the

trial is blinded or not, whether the progression is assessed by independent reviewers or not, the frequency of evaluations that are performed, precisely how progression is defined in the protocol, all of those issues.

So, I think that as a general discussion of time to progression, those are the kinds of issues that are recurring themes in our discussions, and as studies go forward and are proposed to the agency in the future, I think none of us would like to see a dismissal of time to progression as an endpoint, but we would like to see a very rigorous test for time to progression.

MR. MOYER: I just was wondering whether the panel was aware that in 2962, the primary endpoint was progression-free survival. That was independently reviewed by a third party group, and criteria were set forth in that protocol, how to assess that, so when you made that statement, I wasn't sure whether this committee realized that that was the case, part of the case in that study.

DR. SCHILSKY: That was pointed out to us in your briefing document, but thank you for pointing it out again.

I think we need to go on a discussion of the questions at this point. We have three questions that have been posed. I am not going to read through this material in detail.

I would point out that for the first question,

there are three summary tables that are provided. The first table summarizes the efficacy that has been presented from the randomized trials and, in essence, demonstrates that with respect to overall survival, that there is no statistical benefit for the oxaliplatin-containing arms in either of the randomized trials.

In fact, in the 2961 trial, there is actually an approximate two-month deficit in survival for the oxaliplatin arm, whereas, in the 2962 trial, there is an approximate one-month advantage to oxaliplatin, but in neither study is survival statistically significantly different between the arms.

There is statistically significant improvements in response rate and progression-free survival in both of the randomized trials, and in both of the randomized trials, the improvement in progression-free survival is on the order of three to four months.

We then have a brief summary of the other clinical benefit parameters that we have already discussed, and then we have two tables summarizing the adverse event profile from each of the randomized trials.

The first question reads as follows: Both studies show increased response rate and progression-free survival with the addition of oxaliplatin, but neither shows a survival advantage using the protocol specified primary

analysis.

In general, the Oncologic Drugs Advisory Committee has recommended that survival be the basis for approval in first-line treatments in colorectal cancer. Although Study 2962, using a biweekly regimen, did not demonstrate a survival advantage employing the log-rank test specified in the protocol as the planned method for analysis, an adjusted analysis did indicate a survival advantage. The principal adjustment was for baseline alkaline phosphatase.

Does the committee believe that Study 2962 with the alternative analysis persuasively demonstrated a survival advantage?

Is there any discussion on that before we vote?

All those who would vote yes, that the adjusted advantage did persuasively demonstrate a survival advantage, all those who would vote yes, please raise your hand.

[No response.]

DR. SCHILSKY: No yes.

All those who vote no?

[Show of hands.]

DR. SCHILSKY: 12 no. That is unanimous then.

Question 2: The 5-FU/leucovorin regimen used in Study 2962 is not commonly used in the United States.

Does the committee believe that the results of Study 2962 can be extrapolated to 5-FU/leucovorin regimens

that are used in the United States?

Is there discussion on that?

DR. D. JOHNSON: I think we need a little clarification. The way I am interpreting this question goes back to I think a question that was asked earlier, is the regimen that was used, or regimens, used in these trials essentially equivalent to regimens used in the U.S.

I think that is what we are being asked. No, we are not being asked? There is some heads bobbing yes and no, and there is some bobbing no.

DR. J. JOHNSON: We are asking if you think that if we added oxaliplatin to standard U.S. regimens that it would be safe and effective.

DR. D. JOHNSON: So, that raises another specter of questions, I mean whole issues, because effectiveness, one might be able to at least extrapolate from; safety, one might have more difficulty.

Do you want to make it a two-part question or what?

I mean because I think that most of us believe that 5-FU regimens, whether one uses the ones used here or what we use in the U.S. are going to be fairly comparable. Clearly, the safety profiles are different, but it doesn't stop people from using different ones.

The question about what oxaliplatin will add to a

U.S. regimen, I guess is more difficult certainly for me to answer.

DR. SCHILSKY: I think we could anticipate the delay of toxicity and it is from what we have seen in terms of what it adds to a regimen in the context of a randomized clinical trial. It is not so clear that it adds anything but toxicity. So, to that extent, it might be fair to extrapolate.

Dr. Sledge.

DR. SLEDGE: Just on a philosophical basis, I have always been uncomfortable with the idea that there are European regimens and American regimens in oncology. I mean there are regimens, and whether or not one uses them in the United States or in France, I suspect one would get roughly similar results. I think we have to be a little bit careful about, you know, invoking the NIH syndrome in these discussions, you are not invented here.

Personally, I don't think there is a hill of beans difference between the de Gramont regimen and the regimens used in the United States, at least from a survival standpoint.

DR. SCHILSKY: But I think we should--I think Dr. Johnson stated it very clearly in terms of what the FDA wants our opinion about and what I think we are concerned about, which is if this drug were available on the market in

the United States, it is likely, given the way American oncologists practice medicine, that it would be combined with other 5-FU/leucovorin regimens other than the regimens for which it has been rigorously tested.

And are we comfortable assuming that in that context that the drug would have, or the regimen would have, a similar toxicity profile and a similar efficacy profile given the fact that there is very limited data and essentially, in fact, the only data that has been presented to us today by Dr. Goldberg suggested that combining oxaliplatin with the Mayo Clinic style regimen is quite a toxic therapy.

So, you know, would we be comfortable assuming that even the toxicity profile used with the infusional regimens would be similar with the U.S. regimens.

DR. SLEDGE: If that is true, all that would imply is that maybe we are using the wrong regimen in the United States.

DR. SCHILSKY: They may be, but that is not the topic for discussion.

DR. SLEDGE: I mean the real question is whether or not this adds any survival advantage because if we believe that it added a survival advantage, we would find some way of incorporating it into American regimens.

DR. SCHILSKY: I think we just voted on that one.

Dr. Lippman.

DR. LIPPMAN: I agree with your comment. It would be very hard to extrapolate on the toxicity issue before doing the study.

DR. HIRSCHFELD: The issue is the integrated, as you stated, and I just want to clarify that every choice that is made by a practitioner is a risk/benefit analysis, and so that's the framing of what this question is after.

DR. SCHILSKY: Dr. Johnson.

DR. J. JOHNSON: I would just say that in view of your answer to Question No. 1, this Question No. 2 has less relevance than if you had answered Question No. 1 differently.

DR. SCHILSKY: Dr. Simon.

DR. SIMON: That is what I was going to say. It sounded like inherent in this question was the assumption that we believe that it was safe and effective in the context of the regimen it was used in, and I don't think we believe that. So, I don't see how to vote on this question.

DR. SCHILSKY: Let me ask the agency then. Are you content with the discussion and it may not be necessary to actually vote on this question then?

DR. HIRSCHFELD: We are content.

DR. SCHILSKY: All right. So, they are content. If you are happy, we are happy.

Question 3. If the committee concludes that Study 2962 demonstrated a survival advantage--well, we haven't concluded that, so maybe we don't need to vote on Question 3 either.

So, no vote is required on Question 3 in view of the vote on Question 1.

DR. D. JOHNSON: Maybe actually the FDA does want an answer to this question, because inherent in this question is relevant to the future, and it goes back to what Dr. Kelsen was dealing with earlier, and that is, is a single trial sufficient in this new era that we are speaking about. No?

DR. BERMAN: No, but I think if the committee wanted to provide us with any comments about what you believe continued development should look like, what you would want to see. The one study/two study question is one we are quite familiar with, but what you would like to see for this particular agent would be of interest to us.

DR. D. JOHNSON: Well, actually, I think that that is probably worth discussing since as was stated, these were well conducted trials, everyone around the table has inferred that they believe this is an active agent, and so what trials might one conduct that would, in fact, lead to approval.

DR. SCHILSKY: David, let me be sure I understand

what it is you want to discuss because the specific question deals with whether or not a single trial would be sufficient for approval in these circumstances.

Is that what you want to discuss, whether one trial would be sufficient?

DR. D. JOHNSON: No, no, that is what I thought, but we were just told no.

DR. BERMAN: We would be happy to dismiss that question.

DR. SCHILSKY: Fine. So, the FDA doesn't want to discuss that question. So, what question would you like us to discuss?

DR. BERMAN: I think we are agreeing.

DR. D. JOHNSON: I am just speaking for myself, and again, as a clinician, I do hold the bias that this is an active drug and I do hold the bias that in order for me to get my hands on an active drug outside of the institution at which I work, we need to have it approved.

So, the question is how might one do so, and I think that is a very relevant question.

DR. SCHILSKY: Well, one way might be to present randomized clinical trial data showing the survival advantage.

DR. D. JOHNSON: Showing the survival advantage. That would be a wonderful thing. Now, since Dr. Kelsen, who

is much more knowledgeable than I about this disease, and my own faculty member just told me that I am an idiot publicly, and it's on record, which is probably true, but it's irrelevant.

We need to figure out a way to do that, and actually I was struck by a point that Dave made earlier, and it seems to me to be a very relevant one, and they have shown data here that begins to at least perk my ears up, and that is if indeed one can convert patients from unresectability to resectability, and that indeed results in a survival advantage, then, that seems to me to be powerfully persuasive data that this drug is worth using upfront.

And if one were able to have a patient population in whom surgeons could agree upfront that a patient was not resectable, and they could be randomized to a study in which this was the variable, and the endpoint was resectability and CR, that would be, I would think--it would be a large study in terms of numbers going in, but the differences that one would have to construct would not be all that great.

Is that possible?

DR. KELSEN: That would be a really hard study to do.

DR. D. JOHNSON: I am sure it would be hard to do.

DR. KELSEN: It would be ideal, but two surgeons

in the same room, looking at the same CT or MR, agreeing that it is unresectable versus borderline resectable versus clearly resectable, I mean we have all been through that conversation many times. That would be a difficult trial.

DR. HIRSCHFELD: Which?

DR. KELSEN: A trial of oxaliplatin versus best supportive care in the U.S. after failure of first-line therapy, very hard to do, very hard to do. I don't think it is going to happen.

Things may happen. We are having an important discussion this afternoon which may change the paradigm. I don't want to anticipate things, but that might, and then you could think about a second-line trial against a variety of different things I could think about in the other arm, and this gets back to the second-line indication that was discussed, which might lead to approval, because this is a potentially very important agent, and I would hate for us to not be able to move it forward.

So, wrestling with it, I don't see a convert to resectability. I think that would be really hard. The adjuvant studies, if they showed survival advantage as Kim suggested, I mean that would settle it, but they are five years down the line until they finish.

Rich's trial may show important endpoints although, without getting hammered, I thought I heard you

mention something about time to progression or failure-free survival. I don't want to get into that again.

So, those would be the ways to do it. Second-line treatment, adjuvant treatment, a treatment done not in the United States against best supportive care after failure to an acceptable first-line regimen, that would be pretty powerful, I would think. That last one would be pretty powerful.

DR. SCHILSKY: We have some ideas for the future. Let me suggest that we adjourn for lunch, and we will reconvene at 1:45.

[Whereupon, at 1:00 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]

AFTERNOON PROCEEDINGS

[1:50 p.m.]

DR. SCHILSKY: We do have some new people around the table, so why don't we begin with another round of introductions briefly. Dr. Albain, do you want to begin.

Introduction of Committee

DR. ALBAIN: Kathy Albain, medical oncologist, Loyola University, Chicago.

DR. MARGOLIN: Kim Margolin, City of Hope, medical oncology and hematology, Los Angeles.

DR. SLEDGE: George Sledge, medical oncology, Indiana University.

DR. D. JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner and consumer representative.

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford, Connecticut.

DR. SCHILSKY: Richard Schilsky, medical oncologist, University of Chicago.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the Committee, FDA.

DR. SIMON: Richard Simon, biostatistics.

MS. FORMAN: Sallie Forman, patient representative.

DR. CHICO: Isagani Chico, FDA.

DR. JUSTICE: Bob Justice, Deputy Division Director, FDA.

DR. WILLIAMS: Grant Williams, medical team leader.

DR. BERMAN: Rachel Berman, Deputy Office Director.

DR. SCHILSKY: Thank you.

Now, I will ask Dr. Somers to read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Richard Schilsky, Dr. Scott

Lippman, Dr. Kim Margolin, Dr. Victor Santana, and Dr. George Sledge.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to note that Dr. Douglas Blayney and Dr. David Kelsen are excluded from participating in all matters concerning Camptosar.

Further, we would like to disclose that Dr. Kathy Albain and Dr. Richard Schilsky have involvements which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which may create the appearance of a conflict.

The Agency has determined notwithstanding these interests that the interests of the Government and the participation of Drs. Albain and Schilsky outweighs the appearance of a conflict. Therefore, they may participate fully in all matters concerning Camptosar.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in

the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. SCHILSKY: Thank you.

Open Public Hearing

I have not been informed of any members of the public who wish to make a statement to the committee, but is there anyone from the public who would like to address the committee at this time?

Yes. Please come to the podium and state your name and whether you have received any support to be here.

MR. NOVATNE: I am Bill Novatne from Genentech. I have a brief question that I hope the committee will consider this afternoon in their discussion that is relevant to companies developing new drugs in colorectal cancer.

That is, assuming that CPT-11 is approved for use in combination with 5-FU/leucovorin for first-line therapy of metastatic colorectal cancer, is the benefit/risk ratio of sufficient magnitude such that all future clinical trials be required to include that as a comparator, or is it likely that a subset of patients with metastatic colorectal cancer will not receive CPT-11 as part of first-line therapy and the trials using 5-FU/leucovorin as a comparator is so justified in that subset?

Thank you.

DR. SCHILSKY: Thank you. That, of course, is a generic question not pertaining to any particular product in development, right?

Let's go on with the Camptosar presentation and Dr. Miller.

NDA 20-571/SE1-009 Camptosar Injection

(irinotecan hydrochloride injection)

Pharmacia & Upjohn Company

Sponsor Presentation

Introduction

DR. MILLER: Good afternoon. My name is Langdon Miller. It is a pleasure for me to be here today representing oncology drug development at Pharmacia & Upjohn. We are delighted to be able to share with you today important efficacy and safety information supporting FDA approval of Camptosar, also known as irinotecan or CPT-11 for the first-line therapy of metastatic colorectal cancer.

[Slide.]

Within the presentation today, we would first like to provide you with background information relating to the use of 5-FU as first-line therapy of colorectal cancer. These data provide the foundation upon which CPT-11 was developed for this indication.

In addition, we also wish to describe the

development of CPT-11 in colorectal cancer and the rationale for application of CPT-11 as a component of first-line treatment.

Thereafter, the primary focus of my remarks will be on the results from two prospective Phase III randomized clinical trials in the first-line therapy of patients with previously untreated metastatic colorectal cancer.

Each of these well-controlled studies document the clinical benefits of CPT-11 in approving tumor control and prolonging survival for patients with metastatic colorectal cancer.

[Slide.]

Finally, after providing overall summary and conclusions, we would be pleased to answer any questions that you may have. Personnel from Pharmacia & Upjohn, from Aventis, as well as investigators who conducted these trials, are here to assist in responding to your questions.

Background

[Slide.]

As has already been discussed today, colorectal cancer represents a major public health problem. There are 130,000 new cases each year in the United States including 95,000 patients with colon cancer and approximately 35,000 patients with rectal cancer.

Many patients are cured by surgery alone, but

approximately 20 percent have metastatic disease at diagnosis and 40 percent will eventually develop metastatic disease.

Progression of metastases leads to death in almost 57,000 patients each year.

For 40 years, 5-fluorouracil has been the mainstay of standard first-line therapy for patients who develop metastatic disease.

[Slide.]

Because it has been the only available therapeutic option, several strategies have been attempted to improve its cytotoxic effects. One method has been coadministration with leucovorin.

This strategy has been assessed in a meta-analysis of nine randomized trials assessing over 1,300 patients. While 5-FU alone produced only an 11 percent response rate, coadministration with leucovorin increased that response rate to 23 percent. However, median survival at approximately 11 months was not altered by the addition of leucovorin. Thus, adding leucovorin to 5-FU significantly improves response rate but not survival.

[Slide.]

It has also been suggested that protracted infusions of 5-FU may offer greater anti-tumor activity. A meta-analysis of this strategy in over 1,200 patients has

been performed.

Again, we find a clear improvement in response rates from 14 percent with bolus therapy to 22 percent with infusional 5-FU. However, there was little change in survival when 5-FU bolus was compared with infusional 5-FU treatment. Thus, infusion of 5-FU increases anti-tumor activity, but median survival has remained at 12 months.

[Slide.]

Clearly, a novel agent with a different mechanism of action has been needed to further improve survival. CPT-11 offers such a treatment. CPT-11 is a topoisomerase 1 inhibitor that has shown consistent activity in metastatic colorectal cancer.

[Slide.]

When given as weekly, single-agent therapy, in the first-line Phase II setting, response rates of around 30 percent and survivals of approximately 12 months have been observed. These trials suggest that CPT-11 offers activity of similar magnitude for that observed with 5-FU and leucovorin in the meta-analysis.

[Slide.]

CPT-11's distinct mechanism of action was clinically proved in the second-line therapy of metastatic colorectal cancer.

[Slide.]

As presented by Pharmacia & Upjohn to this committee in 1998, when single-agent CPT-11 therapy was compared with best supportive care after failure of first-line 5-FU, patients randomized to CPT-11 had significant improvements in survival.

[Slide.]

Similarly, patients randomized to therapy with second-line CPT-11 versus second-line infusional 5-FU also had significant prolongation of survival.

[Slide.]

Taken together, these findings indicate that CPT-11 offers a new and completely different mechanism of action from that of 5-FU. CPT-11 is active as first-line, single-agent therapy. Furthermore, CPT-11 extends survival when used as second-line treatment.

It could be hypothesized that early combination therapy with CPT-11, 5-FU and leucovorin might further improve tumor control and survival.

[Slide.]

With these considerations in mind, three, Phase I studies were performed as a prelude to Phase III testing. The objective of these trials was to determine appropriate doses when CPT-11 was added to existing schedules of 5-FU and leucovorin.

The first of these trials was conducted by Dr.

Leonard Saltz at Memorial Sloan-Kettering Cancer Center, and examined weekly administration of CPT-11 with weekly bolus administration of 5-FU/leucovorin.

This schedule was based on extensive past knowledge of weekly schedules of 5-FU/leucovorin, and the CPT-11 schedule that had been most widely developed in the United States.

This trial also documented that CPT-11 pharmacokinetics were not materially altered by coadministration with 5-FU and leucovorin.

In France, Study F106 evaluated an every-2-week schedule of administration. CPT-11 was given immediately prior to the established de Gramont infusional regimen of 5-FU and leucovorin. This trial confirmed that CPT-11 pharmacokinetics were unaltered by concurrent treatment with 5-FU and leucovorin.

In Germany, Study G101, performed by Dr. Wilke, evaluated the addition of CPT-11 to an existing infusional 5-FU/leucovorin regimen that has been developed by the German Cancer Society, that is known as the AIO regimen.

Pivotal Phase III Controlled Clinical Trials

[Slide.]

These Phase I studies led directly to the Phase III clinical trials program that I will now describe to you.

[Slide.]

Two randomized, Phase III, controlled, international studies have been conducted that document the first-line clinical benefit of combination CPT-11/5-FU/leucovorin in patients with metastatic colorectal cancer.

One of these trials was sponsored by Pharmacia & Upjohn and is designated Study 0038. This trial compared the combination of CPT-11 given with bolus 5-FU and leucovorin that had been developed by Dr. Saltz to the standard Mayo Clinic bolus regimen of 5-FU and leucovorin.

While not the focus of statistical testing, a CPT-11 alone arm was included to document the activity of single-agent CPT-11 therapy in the first-line setting in the context of a multi-center Phase III study.

The other study was sponsored by Aventis and is designated V303. This trial assessed the CPT-11/5-FU/leucovorin regimens developed in the two European Phase I trials and compared them with established 5-FU/leucovorin regimens that are widely used in Europe.

I would now like to describe to you the conduct and results of pivotal trials Study 0038 and Study V303.

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To be included in Study 0038, patients were required to have histologically proven colorectal cancer, unresectable measurable metastatic disease, and an ECOG performance status of 0, 1 or 2.

Patients could not have received prior chemotherapy for metastatic disease. More than one year must have elapsed since the completion of any previous adjuvant 5-FU chemotherapy.

Patients were not permitted to have undergone prior pelvic radiotherapy. An adequate organ function was, of course, required.

[Slide.]

For Study V303, entry criteria were very similar as those for Study 0038 with the two exceptions that are highlighted in yellow. A minimum of six-month interval since prior adjuvant therapy was required in Study V303, whereas, Study 0038 required a 12-month interval, and in addition, Study V303 permitted enrollment of patients who have received prior pelvic irradiation, whereas, Study 0038 did not.

[Slide.]

For Study 0038, treatment was to be continued until tumor progression or the occurrence of unacceptable toxicity. Supportive care was to be uniform in all arms of the study and included atropine for management of cholinergic symptoms, loperamide for the treatment of diarrhea, and antiemetics for the prophylaxis of nausea and vomiting.

Second-line, post-study chemotherapy was

permitted.

[Slide.]

The same general treatment administration and supportive care approach was taken in Study V303 except that patients experiencing diarrhea in the context of severe neutropenia or neutropenic fever were to receive a fluoroquinolone antibiotic.

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The primary endpoint of Study 0038 was time to tumor progression. Other major endpoints included tumor response, survival, safety, and quality of life as assessed by the validated EORTC Quality of Life Questionnaire C30.

[Slide.]

The same major outcome measures were assessed in Study V303 except that in this trial, response rate was the primary endpoint. Again, the EORTC QLQ-C30 was employed for quality of life assessment.

[Slide.]

On-study measurements were performed at regular intervals and included tumor measurements, clinical evaluations, and laboratory assessments. Tumor assessments were obtained uniformly at six weeks for the first four assessments in all arms of Study 0038, and thereafter at 12-week intervals.

After completion of study chemotherapy,

information regarding post-study chemotherapy and survival was obtained approximately every three months.

[Slide.]

In Study V303, the same methods of assessment were employed with tumor measurements performed regularly every six to seven weeks.

[Slide.]

The assumption of Study 0038 was that the CPT-11/5-FU/leucovorin treatment arm would be associated with a 40 percent improvement in TTP relative to the 5-FU/leucovorin treatment arm.

Differences in endpoints were to be compared by means of two-tailed, unstratified tests. It was estimated that 220 patients per study arm were required to meet study objectives.

[Slide.]

The assumptions of Study V303 were that the combination of CPT-11/5-FU/leucovorin would be associated with a 40 percent improvement in response rate. Again, as in Study 0038, differences between the study arms were to be compared by means of two-tailed, unstratified tests.

It was estimated that at least 169 patients per study arm were required to meet the objectives of this trial.

[Slide.]

Patients enrolled to Study 0038 were stratified by performance status, age, time from initial diagnosis, and whether or not they had received prior adjuvant chemotherapy.

Patients were then randomized equally into one of three treatment arms. The focus of the trial was on the assessment of the comparative efficacy and safety of a weekly combination of CPT-11/5-FU/leucovorin with the standard U.S. regimen of Mayo Clinic 5-FU/leucovorin.

While the schedules of 5-FU administration differed, the trial was designed with the knowledge that the 5-FU dose intensity in the combination arm at 333 mg/m^2/week would be lower than the planned 531 mg/m^2/week in the control arm.

This design helped ensure that any incremental benefit associated with CPT-11/5-FU/leucovorin treatment could be attributed definitively to the CPT-11.

[Slide.]

In Study V303, the primary comparison was between infusional therapy given with CPT-11 and the same infusional therapy given without CPT-11. Within each primary treatment group, individual study sites were to determine in advance whether they preferred to use the AIO regimens or the de Gramont regimens.

Once decided, patients at AIO sites were only to

be randomized to receive the AIO regimen with or without CPT-11. Likewise, patients at de Gramont sites were only to be randomized to receive the de Gramont regimen with or without CPT-11.

[Slide.]

The principal investigator for Study 0038 was Dr. Leonard Saltz. The study was conducted at 71 sites in the United States, Canada, Australia, and New Zealand with enrollment occurring between May 1996 and May 1998.

The final cut-off date for survival was December 1999, that is, 19 months after enrollment of the last patient.

[Slide.]

The principal investigator for Study V303 was Dr. Jean-Yves Douillard. The study was conducted at 83 sites, primarily in Europe, with enrollment occurring between May 1997 and February 1998. The final data cut-off date for survival in this study was October 1999, 20 months after enrollment of the final patient.

[Slide.]

The following slides provide an overview of patient enrollment based on patient characteristics and treatment administration in the Phase III studies.

[Slide.]

Study 0038 enrolled and randomized a total of 683

patients with similar numbers of patients in each treatment group. These patients constituted the intent-to-treat population upon which all efficacy analyses were performed.

A few patients were never treated or were treated on another treatment arm of the study. After accounting for these patients, an as-treated population was defined that was analyzed for drug administration, safety, and quality of life.

[Slide.]

Study V303 enrolled and randomized a total of 387 patients. In each arm, one patient was never treated, leaving 198 patients who were randomized to CPT-11/5-FU/leucovorin and 187 treated patients were randomized to 5-FU/leucovorin alone. This group constituted the full analysis population that was the major focus of efficacy analyses in this study.

After accounting for a patient who was treated on the other arm of the study, an as-treated population was derived that was assessed for drug administration, safety, and quality of life.

Approximately one-quarter of patients were randomized to the AIO regimens and approximately three-quarters of the patients were randomized to the de Gramont regimens.

[Slide.]

In Study 0038, the median ages were similar across treatment groups. There was a predominance of males. A greater proportion of men were enrolled to the CPT-11/5-FU/leucovorin treatment arm.

The majority of patients had tumor-related functional compromise as evidenced by performance status of 1 or higher.

[Slide.]

Similar distributions of patients by age were observed in Study V303 as in Study 0038. In this trial, as in Study 0038, there was a greater proportion of men in the CPT-11/5-FU/leucovorin group.

The populations were approximately evenly split between those with normal performance status of 0 and those with compromised function.

[Slide.]

For Study 0038, the disease-related characteristics were well balanced. Colonic primary tumors predominated as might be expected given the epidemiology of this disease. The majority of patients were known to have one involved organ site with metastatic involvement of the liver in approximately 80 percent of the patients.

[Slide.]

For Study V303, there was a greater proportion of patients with rectal cancer in the CPT-11/5-FU/leucovorin

group. The majority of patients were known to have one involved organ site, again with metastatic involvement of the liver in approximately 80 percent of the patients.

[Slide.]

When considering the disease history of the patients in Study 0038, the median time from initial diagnosis of colorectal cancer to randomization was less than two months.

These findings indicate that most patients participating in this trial already had metastatic disease at the time of primary diagnosis of colorectal cancer. Because most patients had initial metastatic disease, only a minority of patients, approximately 10 percent across the treatment arms, had received prior adjuvant 5-FU.

Patients were to be excluded who had received prior pelvic radiotherapy, however, a few such patients were enrolled into the trial.

[Slide.]

Those patients participating in Study V303 also had metastatic disease at the time of primary diagnosis of colorectal cancer, and thus there was again a short median time from initial diagnosis of colorectal cancer to randomization into the trial.

As a consequence, only one-quarter of patients had received prior adjuvant 5-FU. Consistent with the

relatively higher proportion of patients with rectal cancer in Study V303, approximately 20 percent of patients had received prior radiotherapy.

[Slide.]

Based on past studies, several baseline laboratory tests were prospectively designated in Protocol 0038 as potential prognostic factors. The percentages of patients with abnormalities in these parameters were well balanced among the three arms of Study 0038.

[Slide.]

In Study V303, except for white blood count, baseline laboratory values of potential prognostic significance were well balanced between the two treatment arms of this study.

[Slide.]

In assessing treatment administration, the median treatment duration and upper range of treatment duration was longer with combination therapy than with either 5-FU/leucovorin alone or with CPT-11 alone.

In actuality, as in design, the median 5-FU dose intensity in the combination arm at 236 mg/m^2/week was substantially lower than in the 5-FU/leucovorin arm at 457 mg/m^2/week. The CPT-11 dose intensity in each of the CPT-11-containing arms were similar.

Relative dose intensity of 5-FU and CPT-11 were

approximately 70 percent of planned in the CPT-11/5-FU/leucovorin combination arm. Relative 5-FU dose intensity was 86 percent of planned in the 5-FU/leucovorin alone arm.

[Slide.]

In Study V303, as in Study 0038, the median treatment duration was, in general, longer with combination therapy than with 5-FU/leucovorin alone.

Chemotherapy delivery was excellent. The median relative dose intensities were greater than 80 percent for CPT-11 and 5-FU in both the AIO and de Gramont combination treatment regimens.

[Slide.]

I would now like to describe to you the major efficacy and safety results of the two, Phase III studies.

[Slide.]

In both studies, treatment with CPT-11/5-FU/leucovorin provided substantially improved response rates over those observed with 5-FU and leucovorin alone.

With Study 0038, the confirmed objective tumor response rate with combination therapy at 39 percent contrasted with the 21 percent rate in the 5-FU/leucovorin arm. These differences were highly statistically significant with a p-value of less than 0.0001.

The response rate in the CPT-11 alone arm was similar to that with 5-FU/leucovorin alone.

Confirmed objective tumor response rates were also substantially improved for patients in the CPT-11/5-FU/leucovorin arm of Study V303 at 35 percent versus 22 percent. Again, these differences were highly statistically significant with a p-value of less than 0.005.

[Slide.]

Very analogous results were also seen for time to tumor progression. Median TTP was 7 months with CPT-11/5-FU/leucovorin as contrasted with 4.3 months with 5-FU/leucovorin alone.

An unstratified log-rank test indicated that TTP for the intent-to-treat population in the CPT-11/5-FU/leucovorin patients was significantly improved over that for patients receiving only 5-FU/leucovorin with a p-value of 0.004.

Median TTP in the CPT-11 arm at 4.2 months was similar to the 4.3 months observed in the 5-FU/leucovorin alone arm.

The time to tumor progression results in V303 confirmed those in Study 0038, indicating a median TTP of 6.7 months with CPT-11/5-FU/leucovorin as contrasted with 4.4 months with 5-FU/leucovorin alone.

Again, these differences were highly statistically significant with a p-value of less than 0.001.

[Slide.]