This slide graphically represents the Kaplan-Meier curves for time to tumor progression with combination CPT-11/5-FU/leucovorin relative to that with 5-FU/leucovorin alone for Study 0038.

[Slide.]

The TTP results for Study V303 are shown graphically on this slide.

[Slide.]

A multiple regression analysis was performed to evaluate the effect of treatment on time to tumor progression in the context of stratification factors and the other predefined prognostic variables.

As shown here, when significant baseline patient characteristics, such as LDH, number of involved organ sites, performance status, total bilirubin, and hemoglobin were taken into account, combination treatment was even more significantly associated with improved time to tumor progression with a p-value of 0.0001.

The hazard ratio indicates a 36 percent reduction in the risk of progression with combination therapy.

[Slide.]

Using the same Cox regression process in Study V303, the number of involved organ sites and baseline serum LDH also proved to have prognostic significance in this study. When adjusted for these factors, combination

treatment was again highly significantly associated with improved time to tumor progression with a p-value of 0.0001.

The hazard ratio for Study V303 indicates a 41 percent reduction in the risk of tumor progression.

[Slide.]

Most gratifying was that CPT-11/5-FU/leucovorin treatment in both studies benefitted patients in terms of overall survival.

In Study 0038, the median survival with combination treatment was 14.8 months versus 12.6 months among those patients receiving only 5-FU/leucovorin.

When comparing the differences in survival using the unstratified log-rank test, the result was statistically significant with a p-value of 0.042.

As with response in TTP, the median survival of 12 months in the CPT-11 alone group was similar to that in the 5-FU/leucovorin patients.

A survival advantage for early combination therapy with CPT-11/5-FU/leucovorin was confirmed in Study V303. The median survival with combination treatment was 17.4 months versus 14.1 months among those patients randomized to only 5-FU/leucovorin.

When comparing the differences between the curves using the unstratified log-rank test, the result was statistically significant with a p-value of 0.032.

[Slide.]

This slide provides the Kaplan-Meier survival curves for CPT-11/5-FU/leucovorin as compared with 5-FU/leucovorin alone for Study 0038.

[Slide.]

The Kaplan-Meier survival curves for Study V303 are provided here.

[Slide.]

Again, when accounting for the impact of significant prognostic factors of baseline LDH, performance status, white blood count, extent of organ involvement, and total bilirubin in a multiple regression analysis, CPT-11/5-FU/leucovorin treatment was significantly associated with improved survival in Study 0038 with a p-value of 0.0372.

The hazard ratio indicates a 20 percent reduction in the risk of death with combination therapy.

[Slide.]

In Study V303, as in Study 0038, baseline serum LDH, performance status, and extent of organ involvement were of prognostic significance. When these factors were considered, CPT-11/5-FU/leucovorin treatment was again significantly associated with improved survival with a p-value of 0.0365.

The hazard ratio for Study V303 indicates a 23 percent reduction in the risk of death.

[Slide.]

In order to add perspective to the survival results, information regarding post-study therapy was collected systematically with over 90 percent of patients having follow-up information.

Among patients who were treated in the CPT-11/5-FU/leucovorin arm, of Study 0038, 52 percent received some form of second-line therapy. A larger percentage of patients, 70 percent, who were in the 5-FU/leucovorin arm, subsequently received post-study second-line therapy.

Among the patients who received post-study chemotherapy, the types of regimens received were categorized. All together, 56 percent of patients in the 5-FU/leucovorin only arm of the study ultimately received second-line treatment containing CPT-11 either as a single agent or in combination.

[Slide.]

In Study V303, it was again noteworthy that a larger proportion of patients randomized to 5-FU/leucovorin were treated with post-study chemotherapy, 65 percent, then were patients who were randomized to CPT-11/5-FU/leucovorin, 49 percent.

In this study, 34 percent of patients in the 5-FU/leucovorin only arm ultimately received a second-line CPT-11-based regimen.

In this trial, approximately 15 percent of patients in both groups received second-line oxaliplatin therapy.

The data from both studies indicate that first-line combination treatment with CPT-11/5-FU/leucovorin offers a significant survival benefit even though many patients in the control groups of these studies received second-line therapy.

[Slide.]

As might be expected, treatment with CPT-11/5-FU/leucovorin was associated with more Grade 3/4 diarrhea than was Mayo Clinic 5-FU/leucovorin, however, this difference was primarily in the incidence of Grade 3 diarrhea.

Grade 4 diarrhea, largely defined by the need for hospitalization for supportive care, was comparably infrequent in the treatment and control arms of the two trials, at 8 percent with CPT-11/5-FU/leucovorin, and 7 percent with 5-FU/leucovorin alone.

Grade 3/4 vomiting was more common with CPT-11-based therapy, however, it is noteworthy that Grade 3/4 mucositis was quite infrequent with CPT-11-containing treatment occurring in only 2 percent of patients.

By contrast, the Mayo Clinic schedule of 5-FU/leucovorin induced a much higher frequency of severe

Grade 3/4 mucositis at 17 percent.

Similarly, the 24 percent frequency of Grade 4 neutropenia with combination CPT-11/5-FU/leucovorin was almost half that, the 43 percent rate observed in patients receiving Mayo Clinic 5-FU/leucovorin in the control group.

Proportionately, fewer patients experienced neutropenic fever, 7 percent, when contrasting CPT-11/5-FU/leucovorin with 5-FU/leucovorin at 15 percent.

Discontinuations due to adverse events were acceptably low. The incidence of treatment-related death was approximately 1 percent.

[Slide.]

In Study V303, treatment with CPT-11/5-FU/leucovorin was associated with more Grade 3/4 diarrhea than was 5-FU/leucovorin treatment alone. However, as in Study 0038, this difference was primarily in the incidence of Grade 3 diarrhea. Grade 4 diarrhea was again relatively infrequent in the treatment and control arms of the two trials.

Grade 3/4 vomiting and Grade 3/4 mucositis occurred in 6 percent or less of the patients in either treatment arm.

While Grade 4 neutropenia and neutropenic fever or infection were more often seen with CPT-11/5-FU/leucovorin, the rates were less than 10 percent, well below the level

justifying prophylactic colony-stimulating factor support.

Discontinuations due to adverse events were acceptably low, and as categorized by the investigators, the incidence of treatment-related death was less than 1 percent.

[Slide.]

Quality of life measures were assessed regularly throughout Study 0038 and Study V303 using the validated EORTC QLQ-C30 instrument. Compliance with filling in the questionnaire was excellent in both trials.

At FDA request, three scales were prospectively selected as the primary focus of statistical analysis in Study 0038. These were the global health status, the role functioning, and the pain subscales.

In Study V303, the global health status subscale was considered primary.

[Slide.]

Evaluation of changes in the EORTC Global Health Status Quality of Life Scale during the course of the study revealed that, on average, patients had initial improvements in quality of life in both arms of the study, and that these were similar for CPT-11/5-FU/leucovorin-treated patients and those treated with 5-FU/leucovorin alone.

[Slide.]

Similar findings were noted for role functioning

with an improvement for both groups, that while not statistically significant, was perhaps somewhat more prominent for combination therapy.

[Slide.]

For pain, please note that the scale runs in the opposite direction with higher values indicating worse pain scores and lower values indicating better pain scores.

The evolution of the curves over time indicates that patients in both groups had decreases in pain scores during the course of therapy. These changes were not significantly different between the groups, although the decreases in pain seemed somewhat more prominent with combination therapy than with just 5-FU/leucovorin alone.

[Slide.]

In V303, the pattern of the mean change from baseline in the Global Health Status Subscale was similar between the treatment arms, corroborating the Global Health Status findings in Study 0038.

In essence, both studies showed that addition of CPT-11 to 5-FU/leucovorin achieved significant improvements in tumor control and survival without a clear detrimental impact on overall patient quality of life.

**Summary and Conclusions**

[Slide.]

In conclusion, we have presented to you today the

results of two large independently conducted prospective, randomized, adequate and well-controlled Phase III studies that form the basis for approval of CPT-11 as first-line therapy of metastatic colorectal cancer.

Both studies have compared combinations of CPT-11/5-FU/leucovorin with established standard 5-FU/leucovorin bolus and infusional regimens that are widely used in many regions of the world.

[Slide.]

The unique and important body of data from these studies documents that the addition of CPT-11 to 5-FU/leucovorin significantly improves tumor response rates and significantly lengthens time to tumor progression.

Most important, first-line combination treatment was associated with a significant prolongation of survival despite the fact that many 5-FU/leucovorin-treated patients eventually received effective second-line therapy.

[Slide.]

These advantages were achieved with toxicities that are predictable and manageable, in particular without an increase in Grade 4 diarrhea relative to 5-FU/leucovorin alone.

Rates of other Grade 3/4 toxicities were low. In fact, there was actually less Grade 3/4 mucositis, Grade 4 neutropenia and febrile neutropenia with weekly CPT-11/5-

FU/leucovorin relative to Mayo Clinic 5-FU/leucovorin in Study 0038.

[Slide.]

The safety findings appear to be corroborated by the changes in quality of life during the studies. Combination therapy can prolong life without compromising overall quality of life.

[Slide.]

Finally, CPT-11-based combination therapy sets a new survival standard in the first-line treatment of metastatic colorectal cancer.

[Slide.]

The positive clinical benefits established in these studies clearly support approval of an indication for CPT-11 as a component of first-line therapy of patients with metastatic carcinoma of the colon or rectum.

Later this afternoon, the committee will be asked to recommend which regimens should be included in the final package insert. Given the larger body of data supporting the use of the Saltz and the de Gramont combinations, and the relative lack of interest among North American oncologists in the AIO regimen at this time, Pharmacia & Upjohn proposes that only the Saltz and de Gramont regimens be included in the dosage and administration sections of the package insert.

Thanks very much for your attention. My colleagues and collaborators at Pharmacia & Upjohn and Aventis, as well as Drs. Saltz, Douillard, and Wilke will be pleased to answer any questions that you may have.

DR. SCHILSKY: Thank you very much for a well-focused and concise presentation. We appreciate that.

Questions from the committee? Dr. Albain.

**Questions from the Committee**

DR. ALBAIN: I have three different questions or items for discussion, and I want to echo Dr. Schilsky's comment and thank you all for really a superb presentation and a nice prospective identification of stratification variables and modeling.

The first area that I guess I still need a little clarification on how you designed this trial. I thought I was reading a three-arm trial, however, you are presenting really two-arm statistics here. I would like to see the curves of all three arms as designed and the p-value overall for the three-arm trial.

DR. MILLER: The study was designed initially as a confirmation of clinical benefit for the second-line indication, because as you will recall, CPT-11 was approved based on response rate data as second-line treatment.

At that time, we had no randomized trials confirming clinical benefit directly in second line, and so

Study 0038 was designed in conjunction with the FDA to provide clinical benefit.

For that reason, we included three arms to document CPT-11 activity as a single agent and then the combination activity to confirm that it had activity and what the outcomes would be across the three arms.

However, the hypothesis of the trial was always focused only on the combination CPT-11/5-FU/leucovorin versus the 5-FU/leucovorin treatment arm. There was no statistical testing proposed or planned within the study of the combination arm versus any other arm, and no such testing has ever been done.

DR. ALBAIN: I guess this is a unique design. I haven't seen a Phase III trial presented in this way before, and you don't have a curve to show us of all three arms together, overall survival perhaps? I guess where I am going with this is do you need the 5-FU/leucovorin, that is where I am trying to--because you have already presented data that you don't need the leucovorin, yet, the leucovorin is in this, so from your earlier literature review.

DR. MILLER: No, no, please understand. In the literature review, I was indicating that you do need the leucovorin, that the leucovorin increases the response rate from 14 percent to 22 percent.

DR. ALBAIN: But there was no survival difference.

DR. MILLER: No, but it increases the activity and is the standard throughout the world.

[Slide.]

Here, if one looks at--by the way, this p-value applies only to the comparison of CPT-11/5-FU/leucovorin versus 5-FU/leucovorin. The white curve is that for the CPT-11 alone.

DR. ALBAIN: You have no overall p-value to show us?

DR. MILLER: No.

DR. ALBAIN: Was your sample size then determined only by the two-arm comparison?

DR. MILLER: That's right.

DR. ALBAIN: And you just decided to accrue an equal number? You could really have had much less as a small Phase II component in parallel to show the activity of your single agent. You wouldn't have needed so many patients, then, if you are not--

DR. MILLER: That is potentially true, but in multiple discussions with the FDA over this issue, and a lot of debate among all of us, the ultimate decision was to adopt this trial design.

DR. ALBAIN: The next point, the most compelling data you showed was, to me, the amount of patients who got second-line drug in your 5-FU-alone arm, and that, in fact,

this either suggests that it is better to give active agents together upfront versus in sequence, or you have some synergy going on here.

Is there in-vitro synergy data regarding these two drugs, and, if so, could you show that?

DR. MILLER: There are data that suggest that there may be in-vitro synergy between the two drugs. Obviously, the clinical relevance of that is unclear except in the context of a clinical trial like this, and I think that the data clearly document what the outcome will be in the circumstance.

There clearly is precedence, of course, with the notion of moving therapy earlier in treatment, and not saving drugs, saving good drugs for later, as I think Dr. Johnson indicated earlier today.

Obviously, that is the premise behind adjuvant therapy, and there is some precedence even within colorectal cancer from a trial done in Scandinavia where patients who were asymptomatic with metastatic colorectal cancer were randomized to receive either immediate therapy or therapy only upon development of symptoms, and in that study, there were time to tumor progression and survival benefits associated with early therapy.

DR. ALBAIN: I guess if one extrapolated from metastatic breast in a trial conducted by my esteemed

colleague to the right, Dr. Sledge, we did, in fact, learn from that trial that an anthracycline, a taxine, and the combination, it didn't really matter in terms of overall survival at least, so your data is suggesting to me that there may be some synergistic interactions going on here, at least if you can cross diseases like that, and it is not really fair to do so.

The last point I wanted to raise has to do with just a question really. Do you have any data regarding the Mayo regimen with CPT-11 apart from what is in the 6C trial that we heard about this morning, that is ongoing? Do you have any Phase II data?

In anticipation of approval of this, would investigators, even though the package insert is clearly stating which 5-FU regimens to use, be tempted to use the other regimen if they are more familiar with it? What data is out there right now regarding safety? Is there any?

DR. MILLER: Perhaps I can have Dr. Richard Goldberg address that question.

DR. ALBAIN: He's back.

DR. GOLDBERG: I don't quite know how to respond, the response that you got to bring me back up, but in any event, we have done a Phase I trial of a Mayo type regimen, and in that regimen, which was based on sequence-dependent synergy established in the laboratory of Dr. Scott Kauffman

at Mayo Clinic, and which was published in Cancer Research, we found that giving CPT-11 first with a 24-hour interval between the time CPT-11 was administered and 5-FU was administered, was the most advantageous sequence in HCT-29 colon cancer cells grown in culture.

As a consequence of that, we developed a program of CPT-11 on day one, given with 5-FU and leucovorin on days two through five, on an every-three-week schedule. When you actually do the math on that, the dose intensity of the 5-FU is the same as is given on the classical Mayo regimen, which is given every four to five weeks.

We were able to add CPT-11 to that at a dose of 275 mg/$m^2$ given every three weeks, and as you will recall in the Cunningham trial, the dose is 350 mg/$m^2$.

We started at a very low dose in this because we were afraid of the synergistic diarrhea with two agents that gave diarrhea as the principal side effect. As a consequence of that, we enrolled 56 patients in this Phase I study, and there were 10 responses observed in those 56 patients, in patients who had been previously treated.

So, we took that as an indication of activity, and a decision was made actually to move that directly from the Phase I into the Phase III.

DR. ALBAIN: While you are up there, let me ask you this question I was trying to get at before. The

comparison, since you have equal numbers in the three arms, between CPT-11 alone and CPT-11 plus 5-FU, that curve seemed to be in the middle of the other two.

Is there a need for the 5-FU component of this?

DR. GOLDBERG: I believe that there is. You know, the C6 trial that we are running currently has 5-FU and leucovorin as the control arm, and all of the other five experimental arms are being compared to that 5-FU/leucovorin control arm.

One of the crucial determinants of how that study will proceed is what you tell us regarding this issue. We have written into our study a contingency to drop the 5-FU/leucovorin control arm if we feel that we have established a new standard today.

However, my own feeling is that I would like to retain that arm because I would like to clearly establish whether or not the CPT-11 adds anything, and I would also like to definitively--and please check Mortel, don't shoot me down for this--but definitively put the Mayo Clinic regimen in perspective related to the three drug regimens that we now have available.

It is my belief that the Mayo regimen will be superseded by a triple drug therapy, but we need to prove that definitively.

Does that answer your question? You are rolling

your eyes a little.

DR. ALBAIN: No. I don't know quite why no one is giving me that p-value since you obviously must have it, because you have the same number of patients in each arm, and you should be able to do that comparison if you have done the other two-way comparison.

DR. MILLER: One could do that comparison, but that was not the hypothesis of the study, and the comparison was not done for that specific reason.

DR. SCHILSKY: It does seem fairly clear, though, Kathy, from the data that has been presented so far, that CPT-11 by itself is not superior to 5-FU/leucovorin. I mean even though there wasn't a formal comparison, by just looking at the numbers, the numbers in the two single agent arms looked to be quite comparable.

DR. MILLER: The other issue is, of course, that if you look at the response rate data and the time to tumor progression data, that really the increased efficacy is seen with combination versus the single agent therapy with 5-FU, the so-called single agent therapy with 5-FU/leucovorin.

DR. SCHILSKY: Langdon, I have a question I feel sort of compelled to ask based on our discussion this morning, and that is, do you have any information about whether alkaline phosphatase level is prognostic? You didn't seem to include that in your list of your top 10

favorite prognostic factors.

[Laughter.]

DR. MILLER: Well, we read roughly the same papers that everyone else had and came up with a slightly different list that we defined prospectively. In fact, perhaps Nicoletta Pirotta, our biostatistician could comment on that. I think she may have explored that a little bit.

[Pause.]

If tested with alkaline phosphatase, it is a significant prognostic factor, however, if you apply it, add it as a factor to the model that we have developed, it is not retained in the model.

So, the LDH, the number of involved organ sites, performance status add more explanation to the model than does alkaline phosphatase, at least in these circumstances.

DR. SCHILSKY: Thank you.

Dr. Lippman.

DR. LIPPMAN: Again following up on a discussion this morning about the effects of using active salvage therapy, I know it is hard, it would be difficult to tease it out too much, but in the V303, the group that had 5-FU/leucovorin, 34 percent had CPT-11-based therapy afterwards, do you have a sense of how they did in terms of response or outcome, was it different than the other group or did you look at that?

DR. MILLER: We haven't divided that out, because those comparisons are so grossly biased because they are in no possible way randomized, and there is such patient selection by that time, that we just found it impossible.

DR. LIPPMAN: Right, very confounding bias, but the issue of how second-line active therapy is going to affect survival is a big issue to address.

DR. MILLER: Well, we already know that second-line therapy with CPT-11 significantly improves survival based on two randomized trials, so done where bias is removed as a concern.

DR. SCHILSKY: It is gratifying to see that one can demonstrate a survival advantage with an active combination even in the face of significant cross-over to the active drug. I think it very clearly addresses the point that Dr. Kelsen was raising this morning.

DR. LIPPMAN: That was my point, that, in fact, these results probably underestimate the effects.

DR. D. JOHNSON: Actually, Scott, if I may butt in on your question a little bit, it does and it doesn't. But to expand on that, what would be helpful is to see the survival curve of those--you had 56 percent in the 0038 trial and 34 percent in the 303 trial who had gotten 5-FU and leucovorin, and who subsequently got CPT-11.

As you point out, you do have two randomized

trials with a dataset. What was the survival of that group of patients, was it comparable to what was seen in the Cunningham trial, for example? That would be interesting to know.

The reason this is not quite the same is that unlike the trial we heard this morning, where CPT-11 was available for the oxaliplatin failure, it doesn't appear that oxaliplatin was available to the CPT failures here, and therein lies a bit of the difference in this study.

So, you say only about 8 percent or so of the patients got other therapy, and that would seem unlikely even if it were oxaliplatin to make a major impact. Do you have those data?

DR. MILLER: What do you want, the oxali data or the other therapy data?

DR. D. JOHNSON: All of the above. I would like to know what the survival was, like was it comparable to the Cunningham trial after the 5-FU failures got CPT-11, what was the length of survival, median survival? That is one. And, two, how many patients got oxaliplatin, and were there any responders after CPT failures?

DR. MILLER: Well, this is a first-line study, and the analysis focused on what happened during first-line therapy. After the patients went off--

DR. D. JOHNSON: I am just asking if you have any

of those data.

DR. MILLER: I do not have data regarding response rates in second-line in patients who were off-study.

DR. SALTZ: Dr. Leonard Saltz. Just a comment. Aside from the fact that this was off-study and would have, therefore, been a post-facto analysis, remember that for the Cunningham study, entry criteria were defined at the time of consideration of CPT-11.

We really don't have information as to what the appropriateness was for these individual patients, what their performance status was, what their bilirubin was, what their motivation was, what their other physical conditions were.

So, even if that data were to be teased out of the dataset, which to the best of my knowledge it has not, I would be very hesitant to draw very many conclusions from it.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: Understanding very well that survival trumps quality of life, I just wanted to ask a few questions, some of the details of your QOL subset.

You said that compliance was very good for returning quality of life. How good is good, and did you do any statistical analysis, because one of your conclusions is that quality of life was not--I believe it was not worse on

these arms.

I just wanted to know what kind of analysis did you do to make that conclusion.

[Slide.]

DR. MILLER: The data for compliance are shown here. What we did was look at baseline and virtually 100 percent of the patients at baseline filled in their questionnaires, and then during the course of the first 30 to 32 weeks, which we analyzed, there were sufficient patients during that time. The compliance data for Study 0038 here are seen and are quite good.

This represents the range across the various determinations at each visit.

[Slide.]

A slightly different presentation for Study V303, but the compliance data are shown here, and one can see that these are quite good particularly initially in the first several cycles of treatment, and here, as well.

DR. NERENSTONE: What kind of comparisons, what p-values were you looking for, was there any statistical component of your evaluation of QOL differences or trends in differences?

DR. MILLER: Why don't I have the biostatisticians comment on what they did with these.

MS. PIROTTA: Good morning. The analysis for the

quality of life data was based on analysis of variance for repeated measurements. Since it is well known that patients, during the study, tend to withdraw from study due to worsening of their condition, the approach which was suggested in 1992 by Zwingerman was used to have a more complete set of data and to impute missing data for patients who didn't provide evaluation for quality of life because they withdrew from treatment, to have this kind of imputation according to similar pattern showed by patients who showed a similar profile during the study to the patients who showed similar data, who had similar data at some point in time.

This analysis was carried out on the three main points which were identified for Study 0038, which are global health status quality of life, pain subscale and functional role scale. And the p-value was not significant.

DR. SCHILSKY: Would you please state your name for the record.

MS. PIROTTA: My name is Nicoletta Pirotta, biostatistician, from Pharmacia & Upjohn.

DR. SCHILSKY: Thank you.

Other questions? Dr. Simon.

DR. SIMON: The slides you showed, Langdon, didn't indicate how many deaths there were. For example, on each study.

DR. MILLER: The number of events?

DR. SIMON: Yes, events.

[Slide.]

DR. MILLER: The information is shown here for all of the arms. Here are the total n's for the intent-to-treat population and the full analysis population, and, for instance, for survival, here are the number of events that have occurred in each of the groups.

DR. SIMON: This data is up to date as of when?

DR. MILLER: The V303 data, the cut-off date for survival was October of 1999, and for Study 0038, December of 1999.

DR. SIMON: Very good. How was the timing of the analysis determined?

DR. MILLER: The specific timing of the analysis was based on the primary endpoint. In the case of Study 0038, the analysis was timed to--the initial analysis, once 162 events had occurred in each of the CPT-11/5-FU/leucovorin, and 5-FU/leucovorin arms of the study.

Subsequent updated analysis of survival was provided at FDA request, and those are the data that are shown here.

DR. SIMON: Were there any interim analysis?

DR. MILLER: There was one analysis performed in September of 1999, and at that time the p-value for Study

V303 was 0.028, and it was 0.097 for Study 0038, and then at FDA request, three months later, we provided new survival information, and those data are the ones I have shown.

DR. SIMON: So, it changed relatively substantially just over a few months for Study 0038?

DR. MILLER: Well, it did change. I mean the shape of the curve is virtually identical. There are more events, of course, by that time, and so, you know, it probably adds more power to the ability to detect differences.

DR. SIMON: I noticed there was some imbalance with regard to sex, I think in both studies, as I recall. Was that one of the prognostic factors you adjusted for?

DR. MILLER: It was tested in the model, and it was rejected from the model in both trials.

DR. SIMON: Thank you.

DR. MILLER: Another analysis, for instance, rectal cancer versus colon cancer, and so on, those were also all rejected from the model, as well.

DR. SCHILSKY: One other question. I am curious to know, since survival was not actually the primary endpoint in either of the randomized studies, was there independent review of the investigator assessments with respect to response rate in time to progression, and were there any independent monitoring committees involved,

monitoring these trials?

DR. MILLER: There was independent review in Study V303 of the response in time to progression data. There was not independent review in Study 0038, however, FDA audits have been conducted at some of the major occurring sites, and no issues of concern have been determined.

DR. SCHILSKY: Were there monitoring committees involved in monitoring the studies?

DR. MILLER: No.

DR. SCHILSKY: Other questions from the committee?

Dr. Albain.

DR. ALBAIN: I am just curious how the older age group did in terms of safety. Have you looked at the patients over 70 by any chance?

DR. MILLER: I can get that for you.

[Slide.]

The data are categorized here for Grade 3/4 events, for the major toxicity endpoints of diarrhea, vomiting, mucositis, and neutropenia, and this was Study 0038, for example.

So, the combination arm shows relatively little difference between the younger and older patients. Perhaps somewhat more vomiting here. No change in mucositis and in neutropenia, frequency was roughly the same.

[Slide.]

For Study V303, the same data is shown here. Again, no clear or somewhat of an increase in diarrhea, Grade 3/4 diarrhea among older patients, vomiting again perhaps increased, no change in mucositis, and perhaps a modest increase in neutropenia.

DR. SCHILSKY: Any other questions?

Dr. Simon.

DR. SIMON: Censoring for survival in the studies. How many patients were censored for other than administrative censoring? I mean censored either for having been lost to follow-up or was anybody censored for anything other than that?

DR. MILLER: You mean other than the fact that it was the time of the last follow-up?

DR. SIMON: Yes.

DR. MILLER: Virtually no patients were in that circumstance. I would have to check. Let me check.

[Slide.]

Here is an overall disposition chart. For Study 0038, by way of example, you can see that one patient was lost to follow-up on the arm of the study that actually wasn't subject to testing.

DR. SIMON: Just one clarification. What do you mean when you said there was one interim analysis in September on Study 0038, was that a planned interim

analysis?

DR. MILLER: It was the analysis of the study, the original. The NDA was submitted at that time with the study report.

DR. SIMON: It was timed to be a final analysis essentially? It was at the number of events that was stipulated?

DR. MILLER: Based on time to tumor progression.

DR. SIMON: Okay.

DR. SCHILSKY: Any other questions from the committee?

[No response.]

DR. SCHILSKY: Why don't we take a 15-minute break and we will reconvene at 3:15.

[Recess.]

DR. SCHILSKY: Will the committee members please be seated.

Lest anyone think that this committee runs hot and cold, I just want to be sure that you know that we have no control over the temperature in this room.

We will go ahead with the FDA presentation. Dr. Chico.

**FDA Presentation**

DR. CHICO: Good afternoon, ladies and gentlemen.

[Slide.]

This application seems traditional approval of irinotecan as a component of first-line treatment of patients with metastatic colorectal carcinoma. There are three CPT-11 plus 5-FU/leucovorin dosing schedules being proposed based on results of two large randomized clinical trials.

[Slide.]

Currently, there are two approved single agent administration schedules of CPT-11 for the treatment of patients with recurrent metastatic carcinoma after 5-FU/leucovorin.

Traditional approval was granted in the United States after a significant survival advantage was demonstrated with CPT-11 given every three weeks against best supportive care and infusional 5-FU/leucovorin.

[Slide.]

The applicant is proposing approval of three administration schedules of CPT-11 in combination with 5-FU/leucovorin for first-line treatment of patients with colorectal cancer.

The bolus administration regimen was a schedule born out of a Phase I trial using 90-minute infusions of CPT-11 in combination with bolus 5-FU/leucovorin.

The 5-FU is similar to, but less intense, than the Roswell Park regimen since 5-FU is only given for four out

of six weeks with low dose instead of high dose leucovorin.

Two continuous infusion schedules are being proposed. In contrast to the bolus schedule, CPT-11 was added to existing infusional regimens without adjustment in the doses of 5-FU or leucovorin. Therefore, additional increments in efficacy, as well as toxicity, that were known for this existing regimen may be attributed to CPT-11.

[Slide.]

Study 0038 or the U.S. study, as I will designate it from now on just for this presentation, was primarily conducted in the U.S. Data from this study was reviewed to support the use of CPT-11 in combination with bolus administration of 5-FU.

This was a three-arm trial comparing the combination regimen in Arm B with the Mayo Clinic regimen in Arm C. This daily bolus regimen is approved in the United States for the treatment of colorectal cancer.

A third arm for this study treated patients with single agent CPT-11 using the approved schedule.

[Slide.]

Study V303 was primarily conducted in Europe where infusional 5-FU regimens are more popular. Patients were stratified according to the institution preferred infusional regimen, then randomized to the treatment with or without CPT-11. Data supporting the use of CPT-11 in combination

with two infusional schedules of 5-FU/leucovorin will be reviewed.

[Slide.]

The primary efficacy endpoint of the U.S. study was time to tumor progression. During the planning stages, the FDA recommended that survival be the primary or a co-primary endpoint in this study. However, the protocol was formally amended to include survival as a secondary endpoint around the time of enrollment of the last patient on study. Therefore, the cut-off date for censoring and analysis of survival was not prespecified.

[Slide.]

The primary endpoint of Study V303 or the European study was the response rate, however, the sample size for this study was also sized to detect significant differences in time to tumor progression using combined results from the two infusional regimens A1 and A2 versus the control arms B1 and B2. Survival was a prospectively determined secondary endpoint in this trial.

Other efficacy endpoints for both studies were time to treatment failure, quality of life, and changes in the weight and performance status.

[Slide.]

The analysis of data was focused on survival and key safety parameters. This was accomplished by reviewing

data listings, electronic data, case summaries, and case report forms. Other efficacy endpoints were evaluated with emphasis on determining how supportive they are of the major endpoint results.

[Slide.]

As was already elucidated by the sponsor, this slide shows the similarity between the inclusion criteria in both studies, the differences only in two aspects. The European study allowed patients with prior radiation and prior adjuvant therapy was allowed in both studies, however, the diagnosis of metastatic disease would have to be at least 12 months after adjuvant treatment in the U.S. study.

[Slide.]

Patient characteristics were well balanced among treatment arms in both studies. There are more patients with rectal cancer enrolled in the European study, however, similar number of patients received pelvic radiation between the treatment arms. More importantly, multivariate analysis did not identify the diagnosis of rectal cancer as a significant covariate for survival.

[Slide.]

This is the death graph. First, I will be presenting the survival results from each study individually starting with the European study or Study V303.

This graph shows the number of patients who had

died at the time of analysis. Enrollment for this study was until February 1998. The cut-off date for survival analysis was prospectively defined 12 months after, which was on February 1999. This time, however, only 40 percent of the patients in the CPT-11 plus 5-FU/leucovorin arms were dead, and only 51 percent of the patients in the 5-FU/leucovorin arms.

An updated analysis was requested by the FDA to capture more events and to establish a more mature survival curve. We recognize the retrospective nature of this request, but believe that additional information would be helpful due to the small number of events and its role in confirming the evidence for efficacy.

The new cut-off date was October 1999, at which time 64 percent of the patients and 73 percent were dead in Arms A and B respectively.

[Slide.]

This survival curve reflects the most recent cut-off date of October 1999. The survival analysis for the European study by the FDA and the applicant agree, showing a consistent significant survival advantage in favor of CPT-11 plus 5-FU/leucovorin combination.

For the October '99 cut-off date, the median survival was 17.4 months for patients in the CPT-11/5-FU/leucovorin arm and 14.1 months for the 5-FU/leucovorin

arm. Log-rank tests showed a significant difference favoring the combination arm with a p-value of 0.032.

The hazard ratio for Arm A versus Arm B is 0.77.

[Slide.]

This graph shows the number of patients who had died in the U.S. study, or Study 0038, which was open from May 1996 to May 1998. On September 1999, 16 months after enrollment of the last patient, a majority of the patients have already died, 67 percent in the CPT-11 plus 5-FU/leucovorin arm, and 78 percent in the 5-FU/leucovorin arm.

An updated report was also provided to the FDA with an additional three months of follow-up.

[Slide.]

This is the survival curve that reflects the most recent cut-off date. Note that the survival curves almost overlap, then start to separate after 12 months. There was initially a trend towards a survival advantage in favor of the CPT-11/5-FU/leucovorin arm with a difference of about two months in median survival, a p-value of 0.097 during the first follow-up.

The difference in median survival increased the p-value of 0.042 and hazard ratio of 0.8 in favor of the CPT-11 plus 5-FU/leucovorin combination on second follow-up. This finding seems to be consistent with the positive trend

observed with the earlier cut-off date.

[Slide.]

One of the main concerns with interpretation of the survival endpoint there is subsequent use of active agents and cross-over to the presumably active experimental arm. It was particularly interesting to evaluate those patients in the control arms who subsequently received CPT-11 due to its established survival advantage.

A large number of patients treated in the control arms were crossed over to CPT-11 for second-line therapy, approximately 40 percent in the U.S. study and 30 percent in the European study.

Despite this, a statistically significant survival advantage was shown for patients who were treated in the CPT-11-containing arms.

[Slide.]

The median time to progression was significantly longer in the CPT-11-containing arms in both studies. These significant findings are consistent and strongly supportive of the evidence for survival.

In the analysis of time to tumor progression, patients who were taken off study to receive subsequent treatments without documentation of progression were censored instead of being counted as events.

It was therefore a concern from our part that the

results of time to tumor progression might have been overestimated and the robustness of these findings had to be tested.

One approach was to count all events leading to treatment discontinuation as progression, and this was essentially the analysis of time to treatment failure.

[Slide.]

Although time to treatment failure results are not relied upon heavily from a regulatory standpoint, this analysis is probably sensitive to test our question since it has a tendency for underestimation.

Again, the significant results in favor of the CPT-11/5-FU/leucovorin arms in both studies establishes the robustness of the findings in time to tumor progression.

[Slide.]

Tumor response assessments were consistent with other efficacy findings, showing a significant advantage for response rate in favor of the CPT-11 plus 5-FU/leucovorin arms. Note that for the European study, a third party was involved in the assessment of responses in time to tumor progression.

[Slide.]

Remarkable efficacy findings are as follows. There was a consistent survival advantage in favor of the CPT-11 combination with continuous infusion schedules of 5-

FU/leucovorin.

The initial positive trend was supported by a significant advantage in favor of the CPT-11 in combination with bolus 5-FU/leucovorin arm in the U.S. study. In No. 3, these findings are supported by significant differences in favor of the CPT-11 combination regimens in time to tumor progression, time to treatment failure, and response rates in both studies.

One of the issues raised in the European study was the comparability of the two continuous infusional regimens and whether the efficacy results hold true for each of the treatment subgroups.

[Slide.]

Although it was balanced between the two treatment arms, there were disproportionately less patients enrolled in the corresponding AIO regimen.

[Slide.]

This is a table of efficacy for the treatment subgroups in the European study comparing infusional 5-FU/leucovorin without CPT-11. Comparisons of three major efficacy endpoint results of each of the treatment subgroups, because of the small sample sizes, there were only trends in median survival, median time to tumor progression, and response rates in patients enrolled in the CPT-11 plus weekly continuous intravenous infusion of 5-

FU/leucovorin or the AIO subgroup.

However, these positive trends in favor of the CPT-11 subgroups are consistent with the results of the CPT-11 plus biweekly continuous infusion 5-FU/leucovorin regimen subgroups where significant differences were detected in all three efficacy endpoints.

[Slide.]

I will now review the safety data from individual studies. I will also comment on the safety profile of the infusional treatment subgroups in the European study followed by the safety review of the U.S. study.

[Slide.]

The following slide lists some of the most common toxicities observed during treatment in the European study or the V303 study. Note that CPT-11 again was added to existing regimens of infusional 5-FU without dose adjustments during the first cycle.

There was a higher incidence of overlapping toxicities, such as myelosuppression, neutropenic fever, vomiting, diarrhea, asthenia, and alopecia in the CPT-11 plus 5-FU/leucovorin arms.

The incidence of mucositis attributed to continuous 5-FU infusion were comparable. Cholinergic symptoms were exclusively noted in 26 percent of the patients treated in the CPT-11 arm.

[Slide.]

Before I describe the findings in the U.S. study, let me just make a comment on the infusional 5-FU subgroups in the European study, the yellow being the CPT-11 plus weekly infusional 5-FU, and the red being CPT-11 plus biweekly infusional 5-FU.

Grades 3 and 4 neutropenia was higher in the CPT-11 plus biweekly 5-FU/leucovorin, while the GI toxicities were higher, such as vomiting and diarrhea, were more marked in the CPT-11 plus weekly regimen.

[Slide.]

This graph shows the Grade 3/4 toxicity in the U.S. study. Here, the incidence of severe neutropenia and fever with neutropenia was lower in the CPT-11/5-FU/leucovorin arm compared to the 5-FU/leucovorin arm. There are more nausea, more vomiting, more diarrhea, asthenia, and alopecia, but the incidences were similar to the CPT-11 alone arm. There is more mucositis in the 5-FU/leucovorin arm in this study.

[Slide.]

Discontinuation of treatment secondary to toxicity was higher in the CPT-11 plus 5-FU/leucovorin arm in the European study. Rates were similar between treatment arms in the U.S. study.

[Slide.]

In summary, there was additive neutropenia and a greater incidence of febrile neutropenia in the European study with the CPT-11 plus infusional 5-FU/leucovorin combinations, but a lower incidence in the CPT-11 plus bolus 5-FU/leucovorin.

Vomiting, diarrhea, asthenia, and alopecia were higher in the CPT-11 plus 5-FU/leucovorin arms in both studies. There was a lower incidence of mucositis in the CPT-11 plus weekly bolus 5-FU regimen. More patients discontinued secondary to toxicity in the CPT-11 combination regimens in the European study.

The major considerations for approval of this application will be summarized in the following slides.

[Slide.]

First, data from two large, randomized, and well-controlled studies were submitted to comply with requirements. The control arms in each of the studies are well selected and known to most clinicians by far as the most active comparator arms in the United States and Europe.

[Slide.]

Regardless of the control arm, the CPT-11 plus 5-FU/leucovorin combinations showed a significant advantage in overall survival. This difference was consistent in the European study, and in the U.S. study there was an initial trend of an advantage that became significant in favor of

the CPT-11-containing arm.

[Slide.]

Last, but not least, of the considerations is whether the treatments being proposed demonstrate tolerable toxicity profiles. Where a survival advantage was clear in the European study, there was also additive toxicity from the combination.

In contrast, there are fewer neutropenia and fever with neutropenia and mucositis in the CPT-11 plus 5-FU group in the U.S. study. The incidence of GI toxicities were higher, but similar to single agent CPT-11.

[Slide.]

If this application is approved, we would like to seek the advice of the Advisory Committee regarding the appropriate dose/administration schedule to be considered in the label.

It seems clear that the CPT-11 plus weekly x 4 bolus 5-FU/leucovorin schedule, which is Arm B of the U.S. study, should be included since it produced benefit compared to the Mayo Clinic regimen of Arm C, the only 5-FU/leucovorin regimen currently approved in the United States.

It also seems that the CPT-11 plus the biweekly schedule, continuous infusion schedule, should be recommended since it demonstrated a clear survival advantage

compared to an active control.

Whether the CPT-11 plus weekly continuous I.V. infusions should be recommended seems to be debatable because a number of patients were inadequate to independently substantiate the CPT-11 contribution to efficacy.

[Slide.]

I would like to acknowledge all the members of the FDA review team and take this opportunity to commend the applicant for a very well organized NDA submission.

Thank you very much, and we will all be happy to take your questions now.

DR. SCHILSKY: Thank you very much.

**Questions from the Committee**

DR. SCHILSKY: Questions from the committee? Perhaps I can clarify just one thing on your last point regarding which of the European regimens might be recommended, since that is a question for us.

I think the sponsor made it very clear that at this point, they are not proposing that the AIO regimen be included in the labeling. So, having heard that from the sponsor, is that still an issue that you want us to focus on during our deliberations?

DR. CHICO: I don't believe so.

DR. SCHILSKY: Other questions from the committee?

[No response.]

DR. SCHILSKY: Now is your chance. Don't hold back. Okay. Thank you very much, Dr. Chico.

DR. CHICO: Thank you.

**Committee Discussion and Vote**

DR. SCHILSKY: We do have several questions that we have been asked to consider by the agency. Perhaps before we do so, I am might just ask the committee members if there is any general points for discussion that anyone wishes to have.

Dr. Nerenstone.

DR. NERENSTONE: I would like to address this to Dr. Simon. What do you make of the first look at the data, the U.S. data, that was not significant, that then becomes significant three months later? Do you have to adjust your p-value for multiple looks or can you accept the fact that there might be a biologic reason for separation of the curves later than was initially thought by the protocol?

DR. SIMON: Well, it is usually, of course, accepted that at an interim time, you know, earlier on in the trial, if you are doing interim analyses, that you would adjust those p-values and the p-value of the quote, "final analysis" for the interim looks, but a lot of times the final analysis turns out not to be the really final analysis, and I don't think it is really traditional that on

subsequent analyses after that, that people are using adjusted p-values.

My own feeling is I am always happy to see the most recent data even if I am not totally sure, you know, exactly how to interpret the p-value, and so my own take on it, I don't know what exactly to make out of it, the fact that the curves separate later in the U.S. study than they do in the European study, that they don't separate until 12 months.

You know, the p-value, whether it is 0.045, you know, it is borderline, but given that there were two studies that seemed to show pretty much the same thing, I think that we have some confidence in that.

DR. SCHILSKY: Other discussion? Dr. Albain.

DR. ALBAIN: I don't know if this is the right time for this, Rich, but I would be interested in our group's opinion on do they believe that this data establishes a new standard of care such that 5-FU/leucovorin alone arm in any Phase III trial would now be viewed as not wise.

DR. SCHILSKY: I would like to suggest that we discuss that after we make a final disposition on this application. It is not clear at the moment what is the vote.

DR. ALBAIN: All right. Then, I have another

question for Dr. Simon. Back to the design of the study, could you comment on doing one, two-way comparison, but not doing the other, because we were talking about that earlier, in other words, two of the arms have been compared with the p-value, and that's the only p-value we have of this three-arm trial, not powered as a three-arm trial, as a two-arm trial, but yet we have another arm of equal size.

Would it be justified to be able to look at that two-way comparison? It hasn't been done apparently by the sponsor, but could it be done? It's not proposed in the protocol to do so.

DR. SIMON: I am not sure if I totally understand what the point of having the CPT-11 only arm in that study was, but I think the most important thing is if the protocol really did say that the single comparison that was going to be made was that the 5-FU/leucovorin plus CPT-11 versus 5-FU/leucovorin, if that was stated clearly in the protocol, it was not some post-hoc sort of thing, then, I am comfortable with that.

DR. SCHILSKY: Any other points for discussion?

[No response.]

DR. SCHILSKY: Okay. Why don't we go on to the questions then.

Again, I just want to draw your attention to the preamble, if you will. You have a table summarizing the

efficacy and safety results from both of the randomized trials. I don't think we need to rehash this.

It is clear that with respect to efficacy, both studies show advantages with respect to survival, time to progression, and response rate that are statistically significant in favor of the CPT-11-containing arm, and we have heard about the safety data.

So, the first question we are asked to consider is the indication sought by the applicant is for CPT-11 as a component of first-line treatment of patients with metastatic colorectal cancer.

Should CPT-11 in combination with 5-FU/leucovorin be approved for first-line treatment of metastatic colorectal cancer?

Is there any discussion on that before we vote?

[No response.]

DR. SCHILSKY: All who would vote yes, please raised your hands.

[Show of hands.]

DR. SCHILSKY: It looks like it is unanimous.

Any no?

[No response.]

DR. SCHILSKY: So, it is unanimous yes.

Now, the second question actually deals with this issue of what regimens should be recommended, and I think we

can I guess limit this discussion to just the two regimens, the combination arm from the U.S. study and the de Gramont arm from the European study since there doesn't seem to be interest at this point with respect to the AIO regimen.

So, the second question then is: What dosage regimens of CPT-11 plus 5-FU/leucovorin should be recommended in the dosage and administration section of the label? Subpart a. Recommend the CPT-11 plus 5-FU/leucovorin regimen in Arm B of Study 0038.

All those who would vote in favor of recommending that, please raise your hand.

[Show of hands.]

DR. SCHILSKY: There seems to be a unanimous yes.

Subpart b. Recommend the CPT-11 plus biweekly infusional 5-FU/leucovorin or de Gramont regimen in Arm A1 of Study V303.

All who would vote in favor of recommending that, please raise your hand.

[Show of hands.]

DR. SCHILSKY: Again, unanimous yes.

Now, Dr. Albain has requested that we come back to the question of whether this regimen of CPT-11/5-FU/leucovorin should now be considered the standard against which all future regimens should be compared.

Kathy, do you have thoughts about that?

DR. ALBAIN: Yes. I think you would have a hard time justifying in an informed consent situation on a clinical trial, assuming the patient could otherwise receive both of these agents, not to offer them.

We now have two large Phase III trials that have proven its benefit.

DR. SCHILSKY: So, you would feel an ethical obligation to offer this combination regimen to patients as front-line therapy.

DR. ALBAIN: Yes.

DR. SCHILSKY: Other questions? Comments? Dr. Simon.

DR. SIMON: I am not sure why we, as a panel, whether that is really our role to comment on that, but I guess my feeling, if we are going to comment on it, is that I wouldn't feel that that would be the case.

You know, we have basically a risk/benefit situation. You know, there is some benefit. We didn't see some great tail on these curves, you know, all these patients are dying. You know, it is a couple of months median survival improvement, additional toxicity.

I think it should be up to the patient. I think there has to be clear informed consent as in any study of what the available treatments are, but I personally don't see why that arm would have to be included in any first-line

randomized clinical trial.

DR. SCHILSKY: I completely agree with what you said with respect to sort of the general practice of medicine, how might one approach a patient with newly diagnosed metastatic colon cancer.

I think we probably don't want to spend much time discussing that, because people will practice medicine as appropriate in the context of the doctor-patient relationship.

It probably would be useful for the agency and for the industry if we spent a little bit of time talking about whether a 5-FU/leucovorin/CPT-11 regimen should henceforth be the comparator arm in future randomized trials in front-line metastatic colon cancer.

So, maybe we can just keep it in that context.

Dr. Sledge.

DR. SLEDGE: As I understand the data, in the second-line indication, there is a two- to three-month survival advantage. In the front-line indication, we have a two- to three-month survival advantage.

So, you could easily argue that whether you give it as front-line or second-line therapy, it adds two to three months of survival time.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: I don't think we can or should try

to answer this question categorically. I think for any large study, particularly new pivotal registration studies that we are not supposed to talk about, but we all know that that is part of why this came up, that the goals of that study, the mechanism of whatever the comparator is expected to be, all sorts of other things that need to be taken into account.

I mean as a general rule, I would say yes, this should establish the new standard, but I wouldn't want to be held to that for every trial that I was responsible for designing.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: Actually, I brought it up more because of our discussion this morning, because the agency had asked us to comment on how we might design the next trial with the agent we were discussing this morning, and, in fact, would this need then to be the comparator. That is why I brought it up.

DR. SCHILSKY: We don't ordinarily have comment from the sponsor, however, since we have finished the discussion of the application, Dr. Wilke, please join us as a colleague in this discussion.

DR. WILKE: It was just a comment concerning the question if you perform sequential application of CPT-11, whether this really works out, what you might lose if you

give it not upfront. I think you cannot say that.

These two studies show that if you have an average clinical practice it means if you are starting with front-line chemotherapy and then you switch in those patients who are really able to undergo second-line therapy, this did not influence the overall outcome. It did not minimalize the data. It was still in favor of the combination arm.

So, at the moment, it is not clear whether sequential would be better as an up-front combination chemotherapy. This should be a question of future trials as they are currently running in Europe but, before we don't have this trial, I would say at the moment, up-front combination chemotherapy is probably a reference for future trials.

DR. SCHILSKY: Let me just maybe pose one or two other questions to help frame the discussion. I guess one would be it is clear that there are lots of new agents in development, and we certainly hope that there are agents that will be available in the future that will be shown to be safe and effective in treating metastatic colorectal cancer.

One of the questions that I think lots of people are grappling with is in a study that is being designed today, that is going to be presented to some ODAC three, four, five years hence, if the control arm in that study is

a 5-FU/leucovorin, is that going to be viewed at a future time by a different committee to be considered to be a suitable control arm in view of the fact that CPT-11 will now be available as a component of front-line therapy.

The other issue is sort of a practical one, and it is clear that if the FDA follows our recommendation for approval, that company will be out promoting the use of CPT-11 as a component of front-line therapy, will it be practical to conduct randomized trials in the future in which the control arm does not include CPT-11.

What are the thoughts about that? Dr. Johnson.

DR. D. JOHNSON: Actually, I have several comments to make. The first would be that at least in my time on the advisory panel, in the pre-NDA meetings, it has been made I think abundantly clear to me personally that the FDA looks very strongly upon using as a comparator an FDA-approved regimen.

So, rightly or wrongly, that is something that the industry will have to take into account, and if I may give a couple of examples--and this may be especially relevant for Dr. Albain--I know of no ongoing cooperative group trial at the moment that uses an FDA-approved regimen with one exception for the comparator arm, and yet the regimen that is being used primarily is one--

DR. SCHILSKY: In terms of one particular disease,

David, or cooperative group trials in general?

DR. D. JOHNSON: Excuse me, non-small-cell lung cancer.

DR. SCHILSKY: I just wanted to be clear.

DR. D. JOHNSON: I am not sure why that was a question. I mean that is the only real cancer in the world, everything else is simple. So, you know, it depends on what one's goal is, and so I think if that is the FDA's position that only FDA-approved regimens will be acceptable in that setting, then, there is no reason to discuss it.

DR. WILLIAMS: Dr. Johnson, I don't think that is our position anyway.

DR. D. JOHNSON: But that has been my experience, and I am not suggesting it is a position, but that has been my experience, and I actually think it is the position that the FDA generally has to take. I mean why would one accept a non-proved regimen. So, I am not being critical of that position.

DR. WILLIAMS: If you are talking about equivalence, you are probably right. If you are talking about beating something, that is not necessarily true.

DR. D. JOHNSON: Then, the second question becomes is it ethical--with this wise body, and I am actually surprised, Rich, you asked why they asked us, because we are clearly the repository of all knowledge, and so therefore,

if we rule on this, then, it's over, you know, as far as I am concerned--but the answer is, as a clinician, would one be willing to treat one's patient without CPT-11 if FDA goes forward and approves it, and the answer is clearly yes, I think, as Rich said, the risk-benefit ratio, and one has to assess each patient individually and make that decision, provide the information to the patient, which also occurs in the package insert, and then we make decisions about that.

But I think the larger and the more relevant issue is the one you just touched upon, and that is even if that study were to start today, you are looking at, what, four years, five years down the road, and this whole group will have changed by that time, no question, many of whom are sitting on that side of the table, as well as this side of the table, and I think even if we all thought that it was wise to do so, I think another committee may not.

So, it seems to me we have bound the industry out there to some extent. They are going to have to really think long and hard about a justification for not including in good performance status patients--

DR. SCHILSKY: Will it also be practice, because clearly, I think--

DR. D. JOHNSON: Well, I think patients will vote on this.

DR. SCHILSKY: But here is the issue. Any trial

going forward that elects to use 5-FU/leucovorin as the control arm will have to have it very clearly stated in the consent form that the alternative therapy for the patient is 5-FU/leucovorin/CPT-11, which has been shown to be superior to 5-FU/leucovorin in prospective randomized trials.

I think that is a clear ethical obligation that we would have an investigators to patients would be to be sure that they are aware of that alternative. Once stated in the consent form, I would have a real question as to how many patients would be willing to accept randomization to 5-FU/leucovorin.

DR. D. JOHNSON: That is the practice element of this. Now, I agree with you. I think patients will vote.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: I think from a clinical trials perspective, there really isn't any question. I mean there can be some extenuating circumstances and you never say never, but I think this is now the standard arm to which new approaches are compared.

Now, there are studies probably that are ongoing that don't have this as the standard arm, and that will make it more difficult for this committee to evaluate perhaps, but right now, as the study is designed now, I think this is based on safety and efficacy. This is the new standard for clinical trials.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: I was just thinking as Scott said that, that that brings up things about those of us, or people who are participating in the 6C study, and that little line in all those consent forms that we tell patients that if any new findings occur during the time of your participation in the study, we will be obligated to communicate them to you.

Perhaps this is one instance that qualifies for such a finding.

DR. SCHILSKY: Well, I would think it will have some impact on that study with respect to whether the 5-FU/leucovorin control arm can or should be continued as a control arm in that study, and I am sure the investigators, having heard this discussion, will take that into consideration.

DR. WILLIAMS: Rich, I guess that was the critical control arm for which all the comparisons were powered, right? These were not equivalence designs most likely.

DR. SCHILSKY: I believe I heard Dr. Goldberg say earlier that the study was actually designed with the potential to drop the control arm. I think that has been accounted for already in the study design.

DR. SALTZ: There was a lot of discussion in the design of the intergroup study with the understanding that

these data were in the process of maturing and that we might get to this point, and the study did take into account, just as Dr. Schilsky has said, the possibility that if the 0038 study did show to be positive, that the study could drop the 5-FU/leucovorin control arm, and I think that these discussions are obviously along those lines.

DR. SCHILSKY: Any other discussion on this matter from the committee?

[No response.]

DR. SCHILSKY: Okay. Thank you very much.

We will reconvene at 8:00 a.m. tomorrow.

[Whereupon, at 4:00 p.m., the proceedings were recessed to be resumed at 8:00 a.m., Friday, March 17, 2000.]

- - -

# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO